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The American Heart Journal

VOL. 14 DECEMBER, 1937 NO. 6

Announcement

THIS is the last issue of the AMERICAN HEART JOURNAL to appear under the editorship of Dr. Lewis A. Conner. Some months ago he tendered his resignation, which was publicly announced at the annual meeting of the American Heart Association in June, and efforts to induce him to reconsider his decision have been of no avail.

Dr. Conner was the first editor of this JOURNAL; under his leadership it has grown steadily in size, importance, and influence until it stands today as the leading journal in its field—one of which the editor, the publishers, and American medicine may well be proud. Those who have known Dr. Conner, and especially those who have been associated with him in his work, can testify to the enthusiasm and devotion with which he pursued his labors, while the JOURNAL itself bears eloquent testimony to his ability and his high aspirations. Although he frequently consulted the Directors of the American Heart Association for advice and criticism, the actual work was performed almost wholly by him, and he deserves the credit for the development, the splendid growth, and the high ideals of the JOURNAL. To say this is not to disparage the contributions of his associate editors through many years, Dr. Evelyn Holt and Dr. Hugh McCulloch, who have given so freely of their time and thought, nor that of Dr. Irving S. Wright, who for the past two years has edited the papers on vascular disease with great knowledge and enthusiasm. Without the devoted support of these able associates Dr. Conner could never have achieved what he has, but they have been the first to praise his leadership, his ability, his wisdom, and his unselfish willingness to share their labor whenever necessary.

The Board of Directors of the American Heart Association, keenly sensible of Dr. Conner's unselfish devotion and magnificent achievement, wish to take this opportunity publicly to express their grateful and lasting appreciation of his almost unique service. It is their belief, shared by all who know him, that the American Heart Association and the AMERICAN HEART JOURNAL have been peculiarly fortunate in having as the first editor a man so highly endowed with the qualities that

have made him a distinguished leader in American medicine. As he relinquishes the editorship of the JOURNAL which he has served so loyally and unselfishly, the American Heart Association through its Board of Directors expresses to him its deep gratitude, its warm hope for many happy years of profitable activity, and its sense of continuing dependency upon his wise counsel.

* * * * *

The American Heart Association and The C. V. Mosby Company have the honor of announcing that Dr. Conner's successor as editor-in-chief of the AMERICAN HEART JOURNAL will be Dr. Fred M. Smith, Professor of Medicine in the State University of Iowa. There are probably few men in the field of cardiovascular disease who have as many warm friends in the medical profession, and they will rejoice at this recognition of his ability and influence. His many contributions to our knowledge of heart disease and its treatment are so well known throughout this country and abroad that no word is needed as to his qualifications for this distinguished position. He will have as associate editors Drs. Horace M. Korns of Iowa City, Hugh McCulloch of St. Louis, and Irving S. Wright of New York City.

The publishers of the JOURNAL and the Association of which it is the official organ welcome Dr. Smith to his new post, confident of his ability to continue the splendid work of his predecessor, and bespeak for him and his associates the same fine support and cooperation that were accorded Dr. Conner.

H. M. MARVIN.

Original Communications

A STUDY OF THE RENAL ARTERIES IN RELATION TO AGE AND TO HYPERTENSION*†

ROBERT H. WILLIAMS, M.D., AND TINSLEY R. HARRISON, M.D.
NASHVILLE, TENN.

THE concept that the kidney is responsible for most of the clinical instances of hypertension was at one time widely held. With the more general use of the sphygmomanometer and following the development of methods of estimation of renal function, it became clear that, while in patients with glomerular nephritis the increase in blood pressure is clearly secondary to renal diseases, the more common types of hypertension are frequently encountered in persons who display only minimal evidence of functional impairment of the kidneys and exhibit no striking gross anatomical abnormalities of these organs at autopsy. Thus the concept of "essential" (i.e., nonrenal) hypertension gradually developed, and most pathologists as well as the great majority of clinicians have accepted this general idea.

Quite recently interest in this question has been again aroused by the work of Goldblatt and his associates,[1] which has been confirmed by several different investigators,[2-5] and which has shown that experimental interference with the renal blood supply in dogs can cause persistent hypertension without evidence of significant change in renal function. Since these animals present a symptom-complex which resembles that of essential hypertension in man and since patients with the latter condition usually display abnormalities in the renal arteries, it appears that the whole subject of the relationship between elevated blood pressure on the one hand and renal arterial disease on the other hand should be investigated further. The present report represents an attempt to approach this problem from the histological standpoint.

SELECTION OF MATERIAL

A group of 10 subjects between the ages of fifty and seventy-five years were studied. This age group was chosen as it was wished to note the effects of long-standing hypertension. To study the changes in cases of more rapidly developing and more severe hypertension, a group of 10 subjects with malignant nephrosclerosis were chosen be-

*From the Department of Medicine, Vanderbilt University, Nashville, Tenn.
†This study was aided by the Division of Sciences of the Rockefeller Foundation.

Table I

Changes in the Renal Vessels and in the Glomeruli in Relation to Age and to Hypertension

Group		Age (yr.)			Arterial blood pressure			Weight of both kidneys (gm.)			Weight of heart* (gm.)		
		Highest	Lowest	Mean	Highest	Lowest	Mean	Highest	Lowest	Mean	Highest	Lowest	Mean
Normal blood pressure	Young	27	20	*23*	128/82	80/60	*111/71*	460	270	*325*	310	175	*241*
	Intermediate	40	31	*36*	150/85	95/65	*117/75*	550	255	*362*	350	200	*266*
	Elderly	73	51	*64*	130/80	80/40	*114/68*	400	235	*322*	410	200	*295*
Hypertension	Young: glomerular nephritis	32	21	*28*	210/140	160/100	*182/119*	610	90	*204*	600	295	*407*
	Intermediate: malignant hypertension	40	31	*38*	250/170	180/120	*216/141*	350	220	*284*	860	400	*539*
	Elderly: benign hypertension	73	52	*62*	220/160	160/95	*195/117*	400	270	*312*	930	430	*644*

*The values for the weight of the heart of patients with cardiac valvular disease are not included.
†A value of 100 would indicate that all structures showed the change in question to a marked degree. See text for method of calculation.
‡This refers to the average number of glomeruli in a low power field 4.2 x 3.2 millimeters in diameter.
§When the weights of the kidneys are considered this figure is 24.

TABLE I—Continued

CHANGES IN THE RENAL VESSELS AND IN THE GLOMERULI IN RELATION TO AGE AND TO HYPERTENSION

GROUP		DEGREE OF NARROWING† OF RENAL ARTERIAL TREE									NUMBER OF GLOMERULI‡			PERCENTAGE OF GLOMERULI SHOWING								
		LARGE ARTERIES			SMALL ARTERIES			AFFERENT GLOMERULAR ARTERIOLES						INTRACAPILLARY HYALINIZATION			THICKENING OF CAPSULE			CONTRACTION OF TUFT		
		HIGHEST	LOWEST	MEAN	HIGHEST	LOWEST	MEAN	HIGHEST	LOWEST	MEAN	HIGHEST	LOWEST	MEAN	HIGHEST	LOWEST	MEAN	HIGHEST	LOWEST	MEAN	HIGHEST	LOWEST	MEAN
Normal blood pressure	Young	6.7	0	*1.7*	8.0	0	*1.3*	0	0	*0*	67	40	*47*	1.3	0	*0.3*	1	0	*0.3*	0.7	0	*0.1*
	Intermediate	37.3	0	*19.0*	16.0	4.0	*8.0*	8.0	0	*2.7*	53	28	*43*	3.3	0	*1.0*	1.3	0	*0.6*	1.3	0	*0.3*
	Elderly	67.0	36.7	*48.3*	78.7	18.7	*40.0*	42.7	1.3	*13.3*	46	24	*35*	56.3	5.3	*17.3*	23.7	2.7	*8.0*	25.7	0.7	*8.3*
Hypertension	Young: glomerular nephritis	36.7	0	*15.0*	50.3	0	*28.7*	70.7	9.3	*42.0*	80	25	*49*§	97.0	36.0	*79.3*	45.0	2.7	*15.3*	21.3	3.7	*8.7*
	Intermediate: malignant hypertension	73.3	36.7	*55.0*	93.3	74.7	*83.7*	87.3	38.0	*65.0*	50	14	*30*	87.3	46.3	*59.3*	34.7	10.3	*24.3*	36.7	8.3	22.3
	Elderly: benign hypertension	90.0	20.0	*52.7*	97.3	28.0	*70.7*	74.0	29.3	*57.7*	39	19	*28*	97.0	20.7	*45.3*	48.0	12.7	*24.3*	28.0	3.0	*16.3*

*The values for the weight of the heart of patients with cardiac valvular disease are not included.
†A value of 100 would indicate that all structures showed the change in question to a marked degree. See text for method of calculation.
‡This refers to the average number of glomeruli in a low power field 4.2 x 3.2 millimeters in diameter.
§When the weights of the kidneys are considered this figure is 24.

tween the ages of thirty and forty years. Six patients dying between the ages of twenty-one and thirty-two years with chronic glomerular nephritis were analyzed. (In our limited material we could find only six cases which fulfilled all the requirements.) In choosing the latter group, we believed that (1) the changes associated with essential hypertension could be eliminated, (2) comparisons of the changes in "renal hypertension" could be made with those in "nonrenal hypertension," and (3) involutional changes associated with advancing years would be practically absent.

All hypertensive subjects were chosen with the following requirements:

(1) Systolic blood pressure of 160 mm. or above and a diastolic pressure of 95 mm. or above.

(2) Combined weight of kidneys 220 gm. or more (excluding glomerular nephritic group). (It was believed that the kidneys of essentially normal weight were less likely to show changes due to other causes.)

(3) Weight of heart increased.

Three additional groups of ten subjects with ages corresponding to those above, but showing no evidence of hypertension or renal damage, were chosen to evaluate properly the degree of changes due to the age factor alone.

Patients of the three control groups died of miscellaneous diseases which were infectious in nature in most instances. Uremia was the cause of death in all the patients with glomerular nephritis, with terminal congestive heart failure in four of the six instances. Renal insufficiency was likewise the chief cause of death in eight of the ten patients with malignant nephrosclerosis, congestive heart failure coexisting in five instances. The remaining two patients in this group died of apoplexy. In the older hypertensive subjects renal insufficiency occurred twice but was responsible for death only once, the chief cause of death being congestive heart failure in seven instances, angina pectoris in one, and cerebral hemorrhage in the other.

Age.—The ages of the control and hypertensive patients in each of the respective groups corresponded fairly well. There was a slight discrepancy in the young groups.

Blood Pressure.—The values of the blood pressures in the control groups and the hypertensive groups were probably lower than would have been encountered while the patients were ambulatory and not in their terminal illness. As would be expected, the highest values were in the malignant group. (The values in Table I for the highest and lowest blood pressures do not represent individual measurements but correspond to the highest and lowest general levels of blood pressure observed in any single patient in the respective groups.)

Kidney Weights.—The greatest weights were in the intermediate control group. This was probably due to the fact that the body weight was greatest in this period. It may be noted that the kidney weights of the essential hypertensive groups were approximately normal. Bell[6] has pointed out that in 75 per cent of the patients with essential hypertension the kidneys show no contraction. A significant degree of contraction of the kidneys was found only in the group of glomerular nephritis.

Heart Weight.—The heart weight was greatest in cases of benign nephrosclerosis. This was most likely due to the fact that the hypertension in this group had been present over a longer period. That age also played a part is shown by the control group.

METHOD OF STUDY AND RESULTS

Routine sections obtained at autopsy and stained with hematoxylin and eosin were studied. In each section were examined ten large arteries (chiefly interlobar), twenty-five small arteries (chiefly arcuate and interlobular), and fifty afferent glomerular arterioles. The amount of thickening of the walls with resulting decrease in size of lumina was classified as normal, slight, moderate, or marked. (Such a method is obviously rough as a quantitative approach, but all the sections were studied by the same observer.) For purposes of comparison the vessels showing slight changes were given the value of ⅓, moderate changes a value of ⅔, and marked changes a value of 1. The numbers were added together for the arteries of a given size in a given section and multiplied by the expression 100/number of arteries counted. Thus, if all the arteries of the group under consideration in a given section showed marked narrowing, the resulting figure would have been 100 and similarly 66.7 and 33.3, if all the vessels had shown moderate or slight narrowing, respectively.

Large Arteries.—Although each of the control groups had essentially the same blood pressure, there was a marked increase in sclerosis with advance in years (Table I and Fig. 1). Even though the glomerular group and benign group had the same blood pressure, there was at least three times as much sclerosis in the latter. However, that hypertension also played a rôle in the causation of sclerosis of these arteries was shown by the degree of sclerosis in the malignant group. Considering this and the fact that the glomerular nephritic group showed much more atherosclerosis than its corresponding control group, one would conclude that hypertension was a factor in the production of renal atherosclerosis. Kirkes[7] and later Traube[7] were apparently the first to claim that hypertension produces atherosclerosis. Yet age was the more important factor in causing those atheromatous changes. Since it has been shown that experimental narrowing, by means of the Goldblatt clamp, of

the large renal arteries will produce hypertension in animals, it is reasonable to assume that sclerosis of these vessels in man, if sufficiently advanced, may produce hypertension.

The fact that renal arterial disease may—rarely—be completely absent (Bell and Clawson,[8] Fishberg[9]) in hypertensive patients is not evidence against this view because there is ample evidence that hypertension is not a disease entity but includes a number of different syndromes. The important points are: that renal ischemia can cause hypertension; that renal atherosclerosis is almost universal in subjects of 60 years of age; that it is much more marked in some subjects than in others; and that there is no good evidence against the assumption that it can be responsible for *some* of the cases of hypertension. According to this conception, senile hypertension may in some instances be due not to a disease per se but simply to an exaggeration of a pathological process which occurs in some measure in all subjects with advancing age. The increased degree of arterial disease in the kidneys of hypertensive patients may therefore be explained in two ways: (1) The hypertension increases the strain on the vessels and thereby causes additional disease. (2) The hypertension develops in the first place because the patient has more arteriosclerotic narrowing of the renal vessels than is usual for his age.

According to this point of view, the degree of interference with the renal blood supply must be regarded as of prime importance. Experimentally, one finds that slight constriction of the renal arteries of a dog with a Goldblatt clamp may cause no rise in blood pressure, but, after a certain point is reached, only slight additional constriction is necessary to produce hypertension. That a significant and measurable degree of interference with the renal circulation does exist in certain patients with renal arteriosclerosis is indicated by the work of various authors who have shown by perfusion methods that the resistance in the kidneys is increased in hypertensive subjects and by other investigators who have demonstrated narrowing of the renal vessels by x-ray photographs after injection. (The literature in this regard has been summarized by Fishberg.[9])

If the opinion advanced above—i.e., that renal atherosclerosis may, when sufficiently marked, be a cause of hypertension—is correct, one would expect that a *vicious cycle* would ensue, the *rise in blood pressure causing more arterial disease, this in turn producing further increase in blood pressure,* etc. Such a conception may possibly account for the progressive nature of glomerular nephritis and of malignant nephrosclerosis once these processes are well established. However, this conception fails to account for the initial rise in blood pressure in young subjects with malignant hypertension and also fails to explain the slowly progressive nature of benign hypertension in the subjects in

whom the initial rise in blood pressure is assumed to be the result of the change in the ageing renal arteries. The slower progression of the disorder in these elderly patients might be accounted for by the assumption that the elderly patient is less sensitive to the same stimulus than the younger subject. An analogy could be drawn here to cardiac

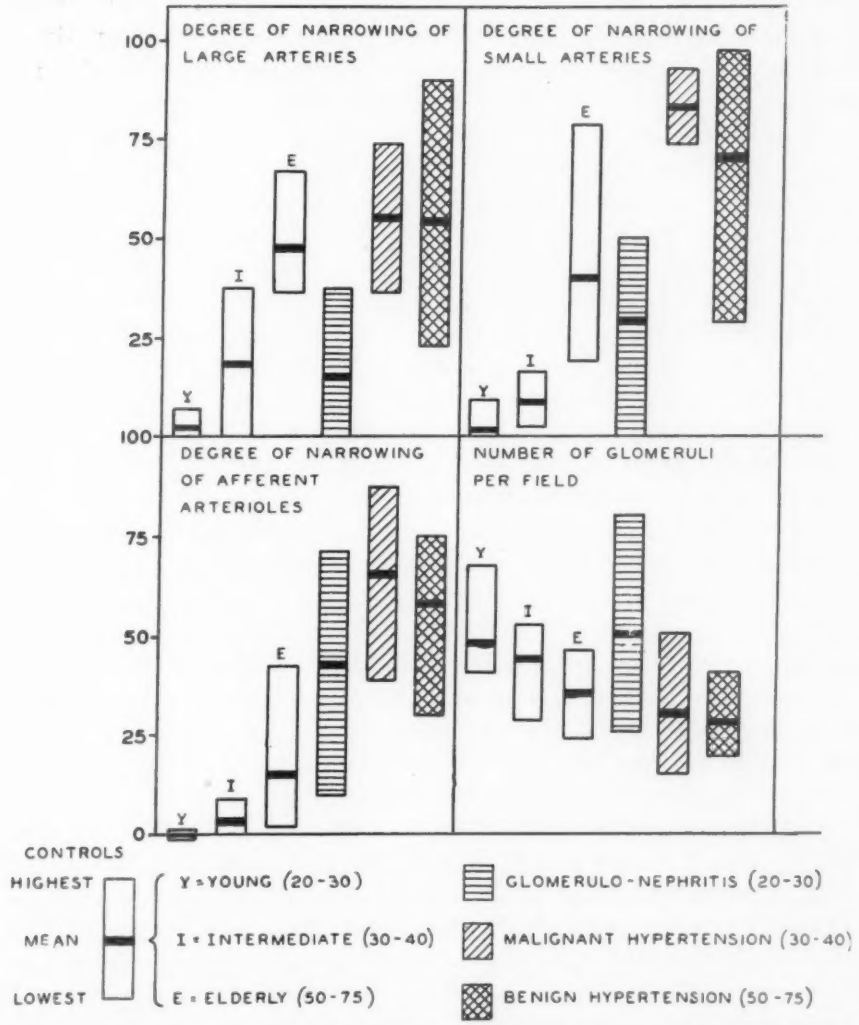

Fig. 1.—The ranges and averages (heavy lines) are shown. The figure shows that narrowing of the large renal arteries is predominantly related to advancing age, while narrowing of the renal arterioles is related chiefly to hypertension. In the case of the small arteries of the kidney both factors are important. There is a progressive decline in the number of glomeruli with advancing years.

dyspnea, for with a given degree of pulmonary congestion, as measured by the vital capacity, a younger person exhibits much greater increase in ventilation and more dyspnea than does an elderly patient. The question whether a given degree of hypertensive stimulus—whatever that

may be—will produce as great a degree of rise in blood pressure in an old subject as in a young one, merits investigation.

Small Arteries.—Our results indicate that the changes in the small arteries with advance in age began at a later stage in life, as the intermediate controls showed relatively little sclerosis and the elderly controls showed a relatively large amount. Hypertension seems to have been the more important factor, as the sclerosis was about ten times as great in the malignant group as in the intermediate controls and twice as great as in the elderly controls. The group with malignant hypertension also showed more disease than the group with benign hypertension, even though the subjects of the latter were much older. However, that age was also significant was shown by the fact that the elderly hypertensive group showed more than twice as much sclerosis as the glomerular group, though the blood pressure was the same. In our cases of essential hypertension there was found some sclerosis of the small arteries in every case. Bell and Clawson,[8] studying a large series of hypertensive cases, found that 98 per cent showed some change in these vessels. This change was noted in all but one of our cases of glomerular nephritis, and in this case the hypertension was of much shorter duration than in the other cases. Fishberg[9] noted that it was most likely to be present in long-standing cases.

Afferent Glomerular Arterioles.—Although there was a definite increase in sclerosis in this group with increase in age, the latter played a very small rôle as compared with the changes associated with hypertension. There was more than three times as much sclerosis in the glomerular nephritic group as in the elderly controls. The subjects with malignant nephrosclerosis, with the highest blood pressure, showed the most outspoken changes. When allowance was made for the great disparity in the ages, the patients with glomerular nephritis had practically as much narrowing of the arterioles as did the individuals with benign nephrosclerosis, the blood pressure being essentially the same in the two groups. Since in the early stages of hypertension noteworthy changes in the blood vessels may not be found, it is believed that the sclerosis is secondary to the hypertension. This opinion is in accord with those of Fishberg and of Bell and Clawson and is strengthened by the work of Blount,[10] who showed that in amphibian larvae in which vasoconstriction was produced by pituitary transplants increase in the size of the heart preceded hyalinization of the basement membrane of the glomerulus.

However, one cannot attribute all the vascular changes in glomerular nephritis to hypertension because the sclerosis of the glomeruli will cause narrowing of the associated arteriole. The relative rôle of this factor may be determined by comparing the changes in the kidneys with those in other organs.

Comparison of the Vascular Changes in the Pancreas and Adrenals With Those in the Kidneys.—As it was desired to compare the vascular changes of the kidneys with those of other very vascular organs, studies were made of the sections of the pancreas and adrenals in five of the previously mentioned elderly subjects and in five of each hypertensive group. Estimations were made of the degree of narrowing of the arterioles in the adrenals and of the small arteries and the arterioles in the pancreas (Table II and Fig. 2).

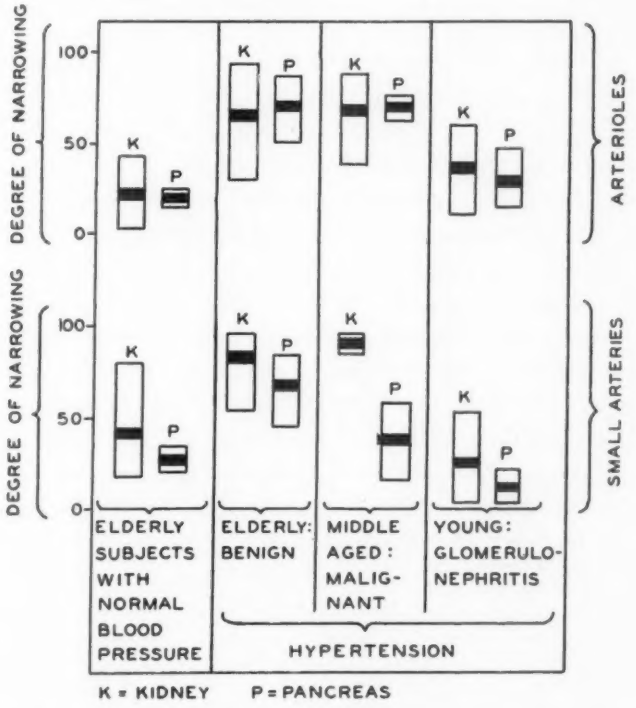

Fig. 2.—In the patients with malignant nephrosclerosis and in those with benign hypertension there appears to be some relationship between arteriolar narrowing and the decrease in the number of glomeruli. No such relationship exists in the elderly control subjects. In none of the groups is there any definite relationship between the degree of narrowing of the large and small arteries and the number of glomeruli.

The changes in the arterioles of the three organs closely paralleled each other.

The small arteries of the pancreas also showed definite narrowing in the elderly controls and in each of the hypertensive groups, but the degree of change was less than that found in the kidneys. Since, on the one hand, there were definite although rather slight changes in the small pancreatic arteries of the young subjects with glomerular nephritis, and since, on the other hand, these vessels also showed definite changes in the elderly control groups, it is evident that in the pancreas

TABLE II

DEGREE* OF NARROWING OF SMALL VESSELS OF KIDNEY, PANCREAS AND ADRENALS

	ARTERIOLES			SMALL ARTERIES	
	KIDNEY	PANCREAS	ADRENALS	KIDNEY	PANCREAS
Elderly controls	22	20	32	43	27
Elderly subjects: Benign hypertension	64	70	68	83	67
Middle-aged subjects: Malignant hypertension	67	69	72	90	38
Young subjects: glomerulonephritis	36	27	30	25	13

*The figures shown represent the average values for five cases. A figure of 100 would indicate that all structures showed marked narrowing.

as in the kidney both age and hypertension may be important factors in the production of degenerative changes in the small arteries.

Types of Histological Change in the Renal Arterial Tree.—Thus far we have considered the degree of narrowing, i.e., the quantitative changes in the vessels. Concerning the qualitative changes we have nothing to add to the descriptions already published by Jores,[11] Fahr,[12] Fishberg[9] and Bell and Clawson.[8] As these authors have pointed out, the changes in the large vessels are predominantly atherosclerotic; those in the small arteries consist particularly of hyperplastic elastic intimal thickening (Jores); and the alterations in the arterioles consist in hyalinization, with necrosis in the acute cases of malignant nephrosclerosis. The vascular changes in glomerular nephritis were similar, although less marked, to those in the other two groups of hypertensive patients, except that the change spoken of by Bell and Clawson as regenerative intimal thickening, which they regard as the result of glomerular occlusion and which consists of delicate fibrous tissue rather than coarse lamellae, was relatively more frequent in this group.

Changes in the Glomeruli.—A study was made of the qualitative and quantitative changes in the glomeruli associated with advance in age and with the previously mentioned types of hypertension. The sections analyzed were the same as those used for the study of the vascular changes.

Under low power were counted the number of glomeruli in several fields, each 4.2 × 3.2 mm. in area, and the average computed. Allowance was made for the reduction in weight of kidneys in the group of glomerular nephritis. Areas showing marked degrees of scarring were not counted. One hundred consecutive glomeruli were counted under high-power magnification, and the degree of capillary hyalinization, thickening of the capsule, dilatation of the capsule, contraction of the tufts and varying combinations of these were recorded. (A few of these changes are noted in Table I. The values given were obtained by calculations similar to those made in the case of the arteries.)

Varying alteration in the glomeruli was noted. The lakelike dilatation of the afferent arterioles, described by Löhlein[13] as being one of the earliest changes associated with hypertension, was frequently noted. The early changes described by McGregor[14]—hyalinization of the capillary basement membrane of the glomerulus—was also often observed. With progression of the disease there occurred varying degrees of capillary hyalinization, thickening of the capsule, and a gradual contraction of the entire glomerulus. The capillary hyalinization was frequently seen to occur alone. Thickening of the capsule occurred alone but rarely. Dilatation of Bowman's capsule with shrinkage of the glomerular tuft has been an infrequent finding. There were only a few glomeruli that did not show some of these changes. There was much more complete scarring of the glomeruli in the group of glomerular nephritis than in other hypertensive cases. The control group showed these changes to a less degree with advance in age.

Moore[15] found that in both man and rat there was a progressive decrease in the number of glomeruli with advancing years. Although our subjects within a given group displayed wide fluctuations the average figures exhibited this general tendency (Table I and Fig. 1).

As a rule, there were fewer glomeruli per field in the hypertensive subjects than in the control individuals within the same age group. When the weight of the kidneys was taken into account, the glomerular nephritic group showed fewer glomeruli than any. The changes in the control groups were relatively rare.

As shown in Fig. 3, there was no definite relationship of the degree of vascular disease to the number of glomeruli in the case of the large and small arteries, but the hypertensive cases seemed to show a definite decrease in the number of glomeruli with advance of the disease in the arterioles. This decrease may be a result of sclerosis of the vessels with resulting atrophy of the corresponding nephron. On the other hand the sclerosis of the vessels may be secondary to involutionary changes in the glomeruli analogous to those described by Grafflin[16] in the daddy sculpin. He found that glomeruli, while present at birth in these fish, gradually disappeared with advancing age and were practically completely absent in the mature adult forms. Alterations similar to those in the sculpin were occasionally seen in our material. *Post hoc, propter hoc,* it may be conceived that an atrophy of a large number of glomeruli might favor the development of hypertension.

Another change which Grafflin described consisted in a pinching of the neck of the tubule, with blockage and swelling of the glomerular capsule and consequent pressure atrophy of the capillary tuft. This was encountered but rarely in our sections.

DISCUSSION

The bearing of the findings on the general conception of essential hypertension may now be briefly discussed. The evidence for the existence of essential (i.e., nonrenal) hypertension consists in the occurrence

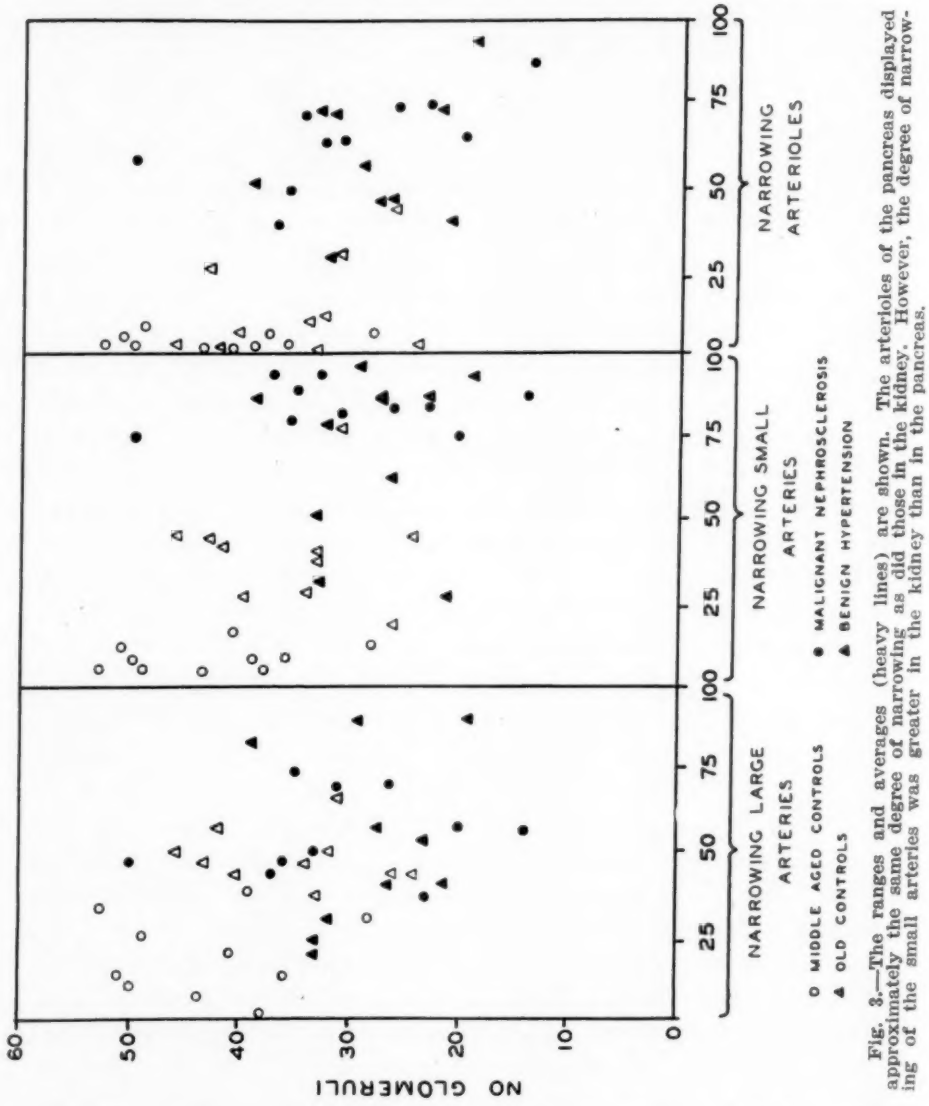

Fig. 3.—The ranges and averages (heavy lines) are shown. The arterioles of the pancreas displayed approximately the same degree of narrowing as did those in the kidney. However, the degree of narrowing of the small arteries was greater in the kidney than in the pancreas.

of a group of patients without a history of antecedent nephritis who present a picture—at least in the early stages of the disease—of elevated blood pressure with no demonstrable impairment of renal function, and who exhibit at necropsy little or no alteration in the gross appearance of the kidney. The clinical evidence is no longer valid, for dogs with experimental renal ischemia and with an increase in blood pressure,

which is obviously of renal origin, may have identical clinical findings. The pathological evidence actually shows that, while in some of the people with essential hypertension changes in the renal vessels may be of such slight degree as to furnish no adequate explanation for the genesis of the increase in blood pressure, in other patients narrowing of the renal vessels similar to but more marked than that which occurs simply with advance in years may be amply sufficient to account for a rise in blood pressure. Such cases are possibly not really essential hypertension at all but belong to the group of renal hypertension, the rise in blood pressure being initially due to a degenerative process in the kidneys rather than to an inflammatory process as in patients with glomerular nephritis.

It is not meant to imply that all essential hypertension is of renal origin. The pathological evidence does not indicate this but only that *some* of such cases *may* be of renal origin. This view is quite different from that advocated by Gull and Sutton,[17] and by numerous later authors, which holds that the increased peripheral resistance of hypertension is dependent on generalized "arteriocapillary fibrosis." It would appear that, when sufficiently advanced, sclerosis of the renal vessels alone can cause hypertension. The rise in blood pressure is clearly not the direct mechanical result of the obliteration of the renal vascular bed, for ligation of the renal arteries does not cause an immediate increase in blood pressure. The mechanism whereby narrowing of the renal vessels produces generalized vasoconstriction remains obscure and requires further investigation.

SUMMARY

A quantitative study has been made of the arteries, arterioles and glomeruli, in sections from the kidneys of elderly subjects with benign hypertension, of middle-aged individuals with malignant hypertension and of young persons with hypertension associated with glomerulonephritis. For purposes of comparison sections from the kidneys of nonhypertensive subjects in the same age groups have also been studied. The chief findings and conclusions are as follows:

1. Narrowing of the large renal arteries is predominantly related to advancing age, the degree of change varying markedly in different subjects. Individuals with hypertension exhibit on the average more change in these vessels than do subjects of the same age dying of other diseases.

2. Narrowing of the afferent glomerular arterioles appears to be mainly the result of hypertension, increasing age being a less important factor than in the case of the larger renal arteries.

3. Narrowing of the small renal arteries is related both to hypertension and to increasing age, neither factor being particularly predominant.

4. The small arteries in the pancreas exhibit less marked narrowing than do those of the kidney.

5. The arterioles in the pancreas and those in the adrenals show approximately the same degree of change as do those in the kidneys.

6. With increasing age there is a progressive decrease in the number of glomeruli per microscopic field, the change being more marked in hypertensive than in nonhypertensive subjects. Narrowing of the arterioles and arteries is one factor, but additional factors also seem to play rôles in the diminution in the number of glomeruli. The possibility that involutionary changes, similar to those occurring in certain lower animals, are also concerned is discussed.

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RESULTS FROM TRICHLORETHYLENE INHALATIONS IN THE ANGINAL SYNDROME OF CORONARY SCLEROSIS*

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IN 1935 Krantz and his coworkers called attention to their experimental work on the pharmacology of trichlorethylene and made the following observations[1-3]: (1) trichlorethylene causes a constriction of the perfused vessels of the frog; (2) it does not affect the consumption of oxygen by rats; (3) it has a variable effect on the coronary blood flow of the dog, at times it increases and at other times it diminishes the blood flow; (4) it decreases the blood pressure and slows the heart rate in dogs; and (5) when applied directly to the sciatic nerve it fails to block the responses of the blood pressure and respiratory system to faradization.

These workers concluded that the drug produces hypalgesia by depressing the basal ganglions and possibly causes a relaxation of the vessels of the splanchnic region while producing peripheral vasoconstriction.

In a recent publication, Love[4] reported his results in the treatment of angina pectoris and coronary thrombosis with trichlorethylene. Twenty-one patients who had the anginal syndrome, including one who had syphilitic aortitis, were treated in this manner. Nine of these patients were said to have had coronary thrombosis at some previous time. Sixteen patients had hypertension. Inhalations were given on the average of three times daily. In eight cases the anginal attacks were completely prevented, in eight other cases the attacks were diminished in severity and frequency, and in one case (syphilitic aortitis) moderate improvement occurred, but antisyphilitic treatment had also been administered. In the four remaining cases no improvement occurred. In three of six cases with coronary thrombosis he claimed to have controlled the pain with inhalations of trichlorethylene at times when administration of opiates had failed to do so.

The interpretation of results in the treatment of the anginal syndrome of coronary sclerosis is extremely difficult and in undertaking to evaluate the merits of any therapeutic program all other modifying procedures must be very carefully considered. Changing the conditions under which the patient lives, such as imposing complete rest in bed or greatly restricting physical activities frequently brings about considerable improvement in the symptoms. Furthermore, individual cases are not strictly comparable owing to the fact that temperament, occupation, habits of life and heredity differ widely in different cases. Likewise, the

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season of the year influences the subjective phenomena of the disease; many patients experience the attacks under less provocation when the weather is extremely cold than they do in the milder seasons of the year.

In undertaking a study of the effect of inhalations of trichlorethylene on the anginal syndrome of coronary sclerosis we were well aware of the difficulties that confronted us in the interpretation of results. We observed forty such patients. The first ones to receive treatment were seen in January, 1936 and the series was concluded in November of the same year, so that sixteen months have elapsed since the beginning and five months since the close of the observation. With only three exceptions, the patients remained ambulatory while under our care. This was done in an attempt to minimize the influence of unusual restrictions, but even so, these patients were away from home and away from their accustomed responsibilities of life and may have been under conditions more conducive to rest and relaxation than would be the case were they treated in their respective communities. They were also perhaps more hopeful as they realized that the form of therapy they were receiving was new in the treatment of an incurable disease.

METHOD OF ADMINISTERING TRICHLORETHYLENE

The method of administering trichlorethylene was carried out uniformly in all cases. Glass ampules, each containing 1 c.c. of the drug, were broken in several layers of gauze and the patient, while in the recumbent position, was permitted to inhale the vapor for exactly two minutes. This procedure was carried out morning and evening for the first week. During the second week it was repeated twice daily on alternate days, and from then on, twice daily for two days each week.

This method of administration was arbitrarily chosen, especially with the intent of caution, as we were dealing with a drug regarding which little experience was available as to its more or less prolonged and repeated use. The presumable industrial hazards of trichlorethylene have been reported by Hamilton[5] and by Eichert[6]; untoward reactions appear to follow the use of the unpure preparations of trichlorethylene for commercial purposes.

The immediate subjective effects of the inhalations were variable. Most of the patients experienced transitory light-headedness or giddiness; some became drowsy, and a few lost consciousness briefly before the inhalation was completed. One patient experienced transient visual hallucinations, and saw what appeared to him as myriads of small brightly colored balloons. In only one case did evidence of intolerance to the drug become evident; the patient, who was a man, had a small macular eruption which was distributed diffusely over the body. This appeared on the third day and disappeared when the inhalations were discontinued. Renewed administration of trichlorethylene was well tolerated.

Our observations were limited entirely to patients who had the anginal syndrome of coronary sclerosis (forty cases). The study did not include cases of acute coronary thrombosis although four patients previously had had this condition.

RESULTS OF TREATMENT

Cases in which varying degrees of improvement occurred (eighteen cases, 45 per cent).—CASE 1. A Jew, aged fifty-seven years, who ran a boarding house, had suffered from anginal attacks for three years. The attacks had recurred three to four times daily after walking only three or four blocks. A roentgenogram showed calcification of the arch of the aorta; an electrocardiogram revealed diphasic T-waves in Lead II, negative T-waves in Lead III and lengthened Q-waves in Lead III. There was no history of previous coronary thrombosis. The value for the systolic blood pressure was 108 mm. of mercury and that for the diastolic pressure was 76 mm. After nine days of treatment, the frequency of the attacks decreased. After the lapse of one year there has been a diminution of both the frequency and the severity of his effort pain, and he is able to walk six to seven blocks without discomfort. Improvement was only moderate.

CASE 2. A Jewish fish merchant, aged forty-eight years, had had anginal seizures for three years. Attacks occurred three or four times daily and he could walk only two blocks without stopping. Roentgenological examination did not disclose any abnormalities; an electrocardiogram showed sinus rhythm and lengthened Q-waves in Lead III. The value for the systolic blood pressure was 134 mm. of mercury and that for the diastolic pressure was 94 mm. The patient has continued with the treatment for nine months. The frequency of the attacks has decreased and he can walk farther than he could before. There was no history of previous coronary thrombosis. Improvement was only moderate.

CASE 3. A physician, aged fifty-eight years, who was a stolid type of individual, had suffered from anginal attacks for one year. The attacks had occurred two to four times daily and he had not been able to walk more than two blocks without stopping. A roentgenogram revealed that the heart was slightly enlarged. An electrocardiogram revealed diphasic T-waves in Lead II, negative T-waves in Lead III, and lengthened Q-waves in Lead III. The value for the systolic blood pressure was 130 mm. of mercury and that for the diastolic pressure was 96 mm. He noted marked improvement after treatment had been given for seventeen days, and fifteen months after treatment was started he was able to resume general practice and at the present time he has only mild attacks after unusual effort. There was no history of previous coronary thrombosis. Improvement was marked.

CASE 4. A farmer, aged sixty-six years, had had anginal attacks for seven years. During the last few months before he came to the clinic the attacks had increased in frequency and severity and the patient was admitted to the hospital in status anginosis. Roentgenological examination did not disclose any abnormality. An electrocardiogram showed diphasic T-waves in Lead I, isoelectric T-waves in Lead II, lengthened Q-waves in Lead III and a delayed P-R interval of twenty-four hundredths of a second. Frequent tracings were not altered. The value for the systolic blood pressure was 120 mm. of mercury and that for the diastolic pressure was 80 mm. The patient gradually improved and eleven months after treatment was started he was doing light farm work in spite of admonitions to the contrary. At present, he experiences attacks which are milder and less frequent than they had been. There was no positive evidence of coronary thrombosis although this condition was suspected at first. Improvement occurred in this case.

CASE 5. A Jewish merchant, aged fifty-one years, had suffered from anginal attacks for one year. The attacks had been irregular in occurrence but usually had appeared several times daily, after moderate activity. Roentgenological examination disclosed no abnormality. An electrocardiogram was normal. The value for the systolic blood pressure was 132 mm. of mercury and that for the diastolic pressure was 88 mm. There was no history of coronary thrombosis. The patient obtained complete relief from the attacks and he can now walk a mile. Treatment was continued after sixteen months.

CASE 6. A man, aged sixty-five years, who was an educator and of an intensive type, had experienced anginal attacks for six years. The attacks had occurred daily after moderate effort. Roentgenological examination disclosed no abnormality. An electrocardiogram showed negative T-waves in Lead I. The value for the systolic pressure was 172 mm. of mercury and that for the diastolic pressure was 118 mm. Treatment has been continued for thirteen months and the patient says he has derived remarkable improvement from it. He now experiences only occasional mild discomfort. There was no history of coronary thrombosis.

CASE 7. A janitor, aged sixty-five years, had had anginal attacks for eight months. During the last two months before he came to the clinic the attacks had become more frequent and more severe than they had been and he was admitted to the hospital in status anginosis. Roentgenological examination disclosed no abnormality. The electrocardiogram showed diphasic T-waves in Leads I and II and negative T-waves in Lead III. There was no alteration on subsequent occasions. The value for the systolic blood pressure was 148 mm. of mercury and that for the diastolic pressure was 96 mm. The patient showed gradual improvement and now, after fifteen months, has only occasional mild attacks. There was no positive evidence of previous coronary thrombosis although this condition was suspected at first. Definite improvement occurred in this case.

CASE 8. A physician, aged sixty years, had experienced an anginal syndrome for ten years. The attacks had occurred once or more daily if he had hurried. Roentgenological examination disclosed no abnormality. An electrocardiogram was normal. The value for the systolic blood pressure was 120 mm. of mercury and that for the diastolic pressure was 80 mm. Treatment has been continued, and after a year the attacks are less frequent and are less severe than they had been. There was no history of coronary thrombosis. Moderate improvement occurred in this case.

CASE 9. A farmer, aged fifty-five years, had had anginal attacks for nine months. He had had daily attacks and had been able to walk only three blocks without pain. Roentgenological examination showed that the heart was slightly enlarged. An electrocardiogram was normal. The value for the systolic blood pressure was 164 mm. of mercury and that for the diastolic pressure was 88 mm. He has continued treatment for eight months, and recently reported that his condition was improved. He now can walk half a mile without provoking an attack. There was no history of coronary thrombosis.

CASE 10. A Jewish peddler, aged fifty-six years, had had anginal seizures for two years. He had been able to walk only one block without pain and the attacks had occurred daily. A roentgenogram showed slight calcification of the aorta. An electrocardiogram was normal. The value for the systolic blood pressure was 114 mm. of mercury and that for the diastolic pressure was 78 mm. Seven months after treatment was started the patient reported that his condition was improved, but that he still experienced painful attacks as a result of effort. He now can walk further than he could. There was no history of coronary thrombosis. Slight improvement occurred in this case.

CASE 11. A man, aged forty-nine years, who was an insurance agent, and of a very apprehensive type, had had anginal attacks for four years. He had experienced at least three attacks daily and they had occurred especially after moderate effort and after meals. Roentgenological examination did not disclose any abnormality. An electrocardiogram was normal. The value for the systolic blood pressure was 138 mm. of mercury and that for the diastolic pressure was 84 mm. He has continued the treatment for nine months and reports that he is more active than he had been and that the frequency of the attacks has decreased. There was no history of coronary thrombosis. Moderate improvement occurred in this case.

CASE 12. A merchant, aged fifty-seven years, had had anginal attacks for one year. The attacks had occurred daily and had been brought on by walking two blocks. A roentgenogram showed calcification of the arch of the aorta. An electrocardiogram revealed low voltage T-waves in Lead III. The value for the systolic blood pressure was 122 mm. of mercury and that for the diastolic pressure was 74 mm. He has continued treatment for five months and reports that his activities have been definitely increased when he is not under the stress of his business. There was no history of coronary thrombosis. The improvement in this case was questionable.

CASE 13. A physician, aged fifty years, had had an attack of coronary thrombosis three years before he came to the clinic and had had severe recurrent anginal seizures since. He had been completely incapacitated. He had been unable to walk a block and a half without pain. A muscle flap operation had been performed but painful seizures had continued to recur. Roentgenological examination did not disclose any abnormality. An electrocardiogram revealed diphasic T-waves in Lead III and lengthened Q-waves in Lead III. The value for the systolic blood pressure was 116 mm. of mercury and that for the diastolic pressure was 84 mm. While the patient has continued to have attacks, they are less frequent and severe than they had been and the nocturnal attacks have ceased. He can now walk four blocks. Treatment has been continued ten months. It is difficult to evaluate the results in this case, owing to the presence of a healed infarction and because an operation which was intended to increase the vascularity of the heart had been performed. Slight improvement occurred.

CASE 14. A physician, aged forty-seven years, had had anginal attacks for thirteen months. Coronary thrombosis had occurred eleven months before he came to the clinic. The anginal attacks had occurred three to four times daily after very slight exertion. Roentgenological examination did not disclose any abnormality. An electrocardiogram showed T-wave negativity in Lead I. The value for the systolic blood pressure was 148 mm. of mercury and that for the diastolic pressure was 108 mm. After the treatment had been employed for six months the patient continued to have attacks of pain but believed that he could walk farther than he could before the treatment was started. At times he can walk as far as a mile and a half. Slight improvement occurred in this case.

CASE 15. A housewife, aged sixty-three years, had had anginal attacks for nine years. She had been unable to walk more than a block at a time without producing pain. A roentgenogram showed the heart was slightly enlarged. An electrocardiogram was normal. The value for the systolic blood pressure was 160 mm. of mercury and that for the diastolic pressure was 80 mm. She reported that her condition was improved after treatment had been continued for six months. She still has attacks but they occur less frequently than they did formerly and are less severe. There was no history of coronary thrombosis. Slight improvement occurred in this case.

CASE 16. An unemployed man, aged sixty-six years, had had anginal attacks for a year and a half. Daily pain had been brought on by walking less than two

blocks. Roentgenological examination did not disclose any abnormality. An electrocardiogram was normal. The value for the systolic blood pressure was 158 mm. of mercury and that for the diastolic pressure was 78 mm. He has been taking treatment for seven months and recently reported that his condition was slightly improved. The attacks occur less frequently than they did and he now can walk four blocks. Slight improvement occurred in this case.

CASE 17. A man, aged fifty-eight years, who was an executive, had had anginal attacks for a year and a half. He had had attacks daily, and walking three or four blocks had induced the attacks. Roentgenological examination did not disclose any abnormality. An electrocardiogram was normal. The value for the systolic blood pressure was 168 mm. of mercury and that for the diastolic pressure was 94 mm. The patient has retired from business and is leading a life of leisure; five months after the treatment was started he reported that his condition was considerably improved. The fact that the patient completely altered his mode of living makes the evaluation of treatment in this case very unsafe. There was no history of coronary thrombosis. Improvement apparently occurred in this case.

CASE 18.—A man, aged forty-six years, who was a druggist, had had anginal attacks for seven years. The attacks had occurred several times daily as a result of very slight exertion or excitement. A roentgenogram showed that the heart was moderately enlarged. An electrocardiogram was normal. The value for the systolic blood pressure was 166 mm. of mercury and that for the diastolic pressure was 108 mm. The patient still has occasional attacks but is considerably improved; he has continued treatment for thirteen months. There was no history of coronary thrombosis.

Cases in which moderate improvement occurred early in the course of treatment but was followed by an aggravation of symptoms while the patients still were undergoing treatment (five cases, 12.5 per cent).—CASE 19. A Jewish merchant, aged sixty years, had had anginal attacks for fourteen years. During the last few months before he came to the clinic his symptoms had increased in severity and he had not been able to climb a flight of stairs or to walk a block without pain. Roentgenological examination did not disclose any abnormality. An electrocardiogram showed diphasic T-waves in Lead I. The value for the systolic blood pressure was 130 mm. of mercury and that for the diastolic pressure was 80 mm. For three months after the institution of treatment the patient felt greatly improved and was able to walk six to eight blocks without pain. However, following an acute infection of the upper part of the respiratory tract the symptoms have returned in spite of the treatment. There was no history of coronary thrombosis.

CASE 20. A druggist, aged fifty-two years, had had anginal attacks for three and a half years. He had been able to walk only one block without pain. Roentgenological examination did not disclose any abnormality. An electrocardiogram was normal. The value for the systolic blood pressure was 186 mm. of mercury and that for the diastolic pressure was 110 mm. For a month the attacks decreased in frequency and severity but with the onset of cold weather the attacks were as severe as they had been. The patient went south and noted improvement again. There was no history of coronary thrombosis.

CASE 21. A housewife, aged fifty-five years, had suffered from anginal attacks for two and a half years. She had had from eight to ten attacks daily after very moderate activity. A roentgenogram showed that the heart was moderately enlarged. An electrocardiogram revealed diphasic T-waves in all leads. The value for the systolic blood pressure was 218 mm. of mercury and that for the diastolic pressure was 134 mm. For the first five months after treatment was instituted the patient obtained marked relief, and the frequency of the attacks was decreased

even when activity was increased. However, during the last three months before this paper was written the severity and frequency of the attacks have increased in spite of treatment and decreased activity. There was no history of coronary thrombosis.

CASE 22. A housewife, aged fifty-three years, had had anginal attacks for five years. Two or three attacks had occurred daily, after slight effort. Roentgenological examination did not disclose any abnormality. An electrocardiogram was normal. The value for the systolic blood pressure was 132 mm. of mercury and that for the diastolic pressure was 80 mm. The patient felt greatly improved during the first five months of treatment, but since an acute infection of the upper part of the respiratory tract occurred in the winter, she has noted no further relief from treatment, and the attacks are as severe and frequent as they had been before treatment was instituted. There was no history of coronary thrombosis.

CASE 23. A retired Jewish merchant, aged fifty-nine years, had suffered from anginal attacks for twelve years. He had had from five to eight attacks daily; the attacks had occurred when he had walked less than one block. Roentgenological examination did not disclose any abnormality. An electrocardiogram showed diphasic T-waves in Leads I and II. The value for the systolic blood pressure was 126 mm. of mercury and that for the diastolic pressure was 82 mm. The frequency and severity of the attacks were decreased after the first ten days of treatment, but since then it has been necessary to administer from three to ten tablets of glyceryl trinitrate daily. There was no history of coronary thrombosis.

Cases in which the treatment did not produce any improvement (thirteen cases, 32.5 per cent).—CASE 24. A banker, aged sixty-eight years, had had anginal attacks for three years. At the time of his visit to the clinic, he was experiencing one to two attacks daily; the attacks occurred after slight effort, particularly after the evening meal. A roentgenogram showed that the heart was slightly enlarged. An electrocardiogram was normal. The value for the systolic blood pressure was 180 mm. of mercury and that for the diastolic pressure was 110 mm. There was no improvement whatsoever after treatment had been continued for five months. There was no history of coronary thrombosis.

CASE 25. A merchant, aged fifty-seven years, had had anginal attacks for ten months. He was having two to three anginal attacks daily, after slight effort. Roentgenological examination did not disclose any abnormality. An electrocardiogram showed negative T-waves in Leads I and II and lengthened Q-waves in Lead I. The value for the systolic blood pressure was 106 mm. of mercury and that for the diastolic pressure was 80 mm. He continued the treatment for seven months, but there was no improvement in his condition. There was no history of coronary thrombosis.

CASE 26. A retired mail carrier, aged sixty-one years, had had dyspnea after effort, for one year, and anginal attacks for one week. He had had one or two painful seizures daily, after slight effort. A roentgenogram showed that the heart was slightly enlarged. An electrocardiogram was normal. The value for the systolic blood pressure was 140 mm. of mercury and that for the diastolic pressure was 100 mm. Continued treatment for three months did not produce any improvement. There was no history of coronary thrombosis.

CASE 27. A W.P.A. worker, aged fifty-six years, had had anginal attacks for five weeks. He had had several attacks daily after slight effort. A roentgenogram showed that the heart was moderately enlarged. An electrocardiogram revealed T-wave negativity in Lead I and a left ventricular preponderance. The value for the systolic blood pressure was 166 mm. of mercury and that for the diastolic pressure

was 100 mm. Continued treatment for four and a half months did not produce any improvement. There was no history of coronary thrombosis.

CASE 28. A Jewish painter, aged sixty-three years, had had anginal attacks for fifteen months. Walking slowly for only two blocks had precipitated the painful seizures. A roentgenogram showed that the heart was moderately enlarged. An electrocardiogram revealed a lengthened Q-wave in Lead I and a left ventricular preponderance. The value for the systolic blood pressure was 154 mm. of mercury and that for the diastolic pressure was 100 mm. He continued treatment two and a half months, without improvement. There was no history of coronary thrombosis.

CASE 29. A Jewish tailor, aged forty-eight years, had had anginal attacks for nine months. The attacks had occurred daily and had been induced by walking only one block. Roentgenological examination disclosed no abnormality. An electrocardiogram showed low voltage T-waves in Leads I and II and iso-electric T-waves in Lead III. The value for the systolic blood pressure was 130 mm. of mercury and that for the diastolic pressure was 80 mm. The patient did not obtain any relief from treatment. There was no history of coronary thrombosis.

CASE 30. A man, aged fifty-six years, who was a clerk, first had anginal attacks eight years before he came to the clinic. At the time that treatment was undertaken he had daily attacks when he walked three to four blocks. Roentgenological examination disclosed no abnormality. An electrocardiogram was normal. The value for the systolic blood pressure was 130 mm. of mercury and that for the diastolic pressure was 92 mm. No improvement occurred after six months of treatment. There was no history of coronary thrombosis.

CASE 31. A physician, aged forty-nine years, had had anginal attacks for five years. The attacks had occurred daily and frequently had been induced by walking three to four blocks. Roentgenological examination disclosed no abnormality. An electrocardiogram was normal. The value for the systolic blood pressure was 190 mm. of mercury and that for the diastolic pressure was 130 mm. After three months of treatment the patient did not note any improvement in his condition. There was no history of coronary thrombosis.

CASE 32. A housewife, aged sixty years, had had anginal attacks for two years. The attacks had occurred daily, after she had walked only one block. Roentgenological examination disclosed no abnormality. An electrocardiogram was normal. The value for the systolic blood pressure was 142 mm. of mercury and that for the diastolic pressure was 82 mm. No improvement was noted after three and a half months of treatment. There was no history of coronary thrombosis.

CASE 33. A clergyman, aged sixty-seven years, had had anginal attacks for twenty-two months. The attacks had occurred daily after he had walked only three or four blocks. Roentgenological examination did not disclose any abnormality. An electrocardiogram was normal. The value for the systolic blood pressure was 114 mm. of mercury and that for the diastolic pressure was 86 mm. There was no improvement after one month of treatment. There was no history of coronary thrombosis.

CASE 34. A railway clerk, aged thirty-one years, had had anginal attacks three months. Six weeks before he came to the clinic he was said to have had a coronary thrombosis and had continued to have daily attacks of pain after he had walked only two or three blocks. An electrocardiogram was normal, which throws considerable doubt on the diagnosis of coronary thrombosis. Roentgenological examination did not disclose any abnormality. The value for the systolic blood pressure was 160 mm. of mercury and that for the diastolic pressure was 120 mm. The

patient continued treatment two and one-half months but did not obtain any improvement. This patient's attitude was rather skeptical as he was acquainted with the commercial use of the drug.

CASE 35. A farmer, aged fifty-one years, had had anginal attacks for three years. Daily attacks had occurred after he had walked two blocks. Roentgenological examination did not disclose any abnormality. An electrocardiogram was normal. The value for the systolic blood pressure was 150 mm. of mercury and that for the diastolic pressure was 90 mm. There was no improvement after three and one-half months of treatment. There was no history of coronary thrombosis.

CASE 36. A station agent, aged fifty years, had had anginal attacks for eight years. The attacks had occurred frequently and had been induced by walking three blocks. The attacks had started eight years before he came to the clinic, and they had followed coronary thrombosis. Roentgenological examination disclosed no abnormality. An electrocardiogram showed low amplitude QRS complexes in all leads. The value for the systolic blood pressure was 132 to 170 mm. of mercury and that for the diastolic pressure was 90 mm. No improvement was noted after three and a half months of treatment.

Cases in which death occurred (four cases, 10 per cent).—CASE 37. A Jewish housewife, aged sixty-three years, had had anginal attacks for fifteen years. The attacks had occurred from two to five times daily after very little exertion. The patient had been forced to live a very restricted life. A roentgenogram showed that the heart was moderately enlarged. An electrocardiogram revealed the presence of complete left bundle-branch block (0.16 second) and diphasic T-waves in Lead I. The patient was definitely improved after four and a half months of treatment, but she died very suddenly at that time at her home. Necropsy was not performed.

CASE 38. A lumber merchant, aged sixty-five years, had had anginal attacks for three years. Daily attacks had occurred after he had walked only two blocks. Roentgenological examination did not disclose any abnormality. An electrocardiogram revealed diphasic T-waves in Lead II and negative T-waves in Lead III. The value for the systolic blood pressure was 120 mm. of mercury and that for the diastolic pressure was 80 mm. The patient continued treatment for nine months without benefit, and then died suddenly at his home. Necropsy was not performed.

CASE 39. A salesman, aged forty-five years, had had anginal attacks for two years. The attacks had occurred daily and after he had walked slowly for a very short distance. Roentgenological examination disclosed no abnormality. An electrocardiogram revealed T-wave negativity in all leads. The value for the systolic blood pressure was 134 mm. of mercury and that for the diastolic pressure was 76 mm. He continued treatment four months, without improvement, and death suddenly occurred at his home. Necropsy was not performed.

CASE 40. A station agent, aged sixty-three years, had had anginal attacks for two years. They had occurred several times daily, after slight exertion. A roentgenogram showed that the heart was slightly enlarged. An electrocardiogram revealed incomplete bundle-branch block, diphasic T-waves in Lead I, and low amplitude complexes in all leads. The value for the systolic blood pressure was 106 mm. of mercury and that for the diastolic pressure was 72 mm. The patient had less pain after one month of treatment but congestive heart failure developed and the patient died in his sleep two and a half months after he started the treatment. Necropsy was not performed.

SUMMARY

The results of inhalations of trichlorethylene in this series of cases of the anginal syndrome of coronary sclerosis do not permit this method of treatment to be accepted with enthusiasm. In eighteen cases (45 per cent) varying degrees of improvement occurred. However, when these cases are critically analyzed it is found that only one patient obtained complete relief while the others had fewer attacks of less severity.

In five cases (12.5 per cent), temporary improvement was noted but a return of the previous symptoms occurred while the treatment was still in progress. It is possible that these patients became imbued with a new hope in undertaking this treatment and that their primary response was influenced by this attitude. We, however, were very careful not to create any false hopes among the patients treated. They were frankly advised that the procedure was entirely experimental.

In thirteen cases (32.5 per cent) no improvement whatsoever was noted. The patients in these cases received treatment from one to seven months.

Four patients (10 per cent) died during the course of treatment. All deaths occurred suddenly. Two of the patient who died were temporarily improved.

We have already mentioned the difficulties encountered in the evaluation of the results of therapy in the anginal syndrome of coronary sclerosis. This evaluation is based largely on the interpretation of variations in subjective phenomena. We cannot overlook the natural history of the disease or the fact that similar data have been furnished by many individual observers who have used other drugs in the treatment of this disease.

While the results obtained with this method of treatment have been disappointing, it is however a procedure that warrants a trial when the usual therapeutic agents have failed to give relief. In our experience, and according to the method described, the drug is well tolerated and its administration appears to be perfectly safe.

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HEMODYNAMIC STUDIES IN EXPERIMENTAL CORONARY OCCLUSION*

IV. Stellate Ganglionectomy Experiments

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BASED on certain clinical, anatomical, and experimental considerations recorded in the literature, Cox and Robertson[1] recently reported an experimental study of the effect of stellate ganglionectomy on various hemodynamic functions in dogs. Twenty carefully trained dogs were tested for resting and exercise heart rate, respiratory rate, and blood pressure, and ten of these for cardiac output. All dogs were subjected to ligation of the left anterior descending coronary branch. Prior to coronary ligation, one-half of the dogs were subjected to bilateral stellate ganglionectomy including the removal of several of the upper dorsal ganglia. The surviving dogs were sacrificed several months after the beginning of the experiment, at which time comparisons were made of the size of the infarcts. It was found that occlusion of the left anterior descending coronary branch produced no appreciable differences between the dogs with stellate ganglia intact and those in which they were removed, as regards pulse rate, respiration, or blood pressure. However, the resting cardiac output became persistently elevated in the dogs with intact ganglia, whereas this function was not altered in the ganglionectomized dogs. Death due to ventricular fibrillation immediately after the vascular ligation was less frequent, and the size of the infarcts was generally smaller in the ganglionectomized dogs.

In several recent publications on hemodynamics following acute occlusion of the left anterior descending coronary branch, Gross, Mendlowitz, and Schauer[2-5] have shown that this produces an immediate fall in cardiac output and a delay in cyanide circulation time. Study of control groups in order to determine the effects of anesthesia alone or anesthesia followed by thoracotomy without vascular occlusion, disclosed the fact that the above mentioned hemodynamic changes were greater than could be accounted for by these control procedures, and were consequently due to the vascular occlusion. The pulse rate, venous blood pressure, hemoglobin, erythrocyte count, blood volume, and serum proteins showed no appreciable immediate changes following the vascular occlusion. Experiments on vagosympathectomized dogs indicated

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that the immediate fall in cardiac output was cardiogenic and, therefore, was not influenced by the nervous pathways. All the altered functions in these dogs approached or reached normal values by the end of a week after the vascular occlusion. It seemed of interest, therefore, to determine whether stellate ganglionectomy in dogs produces changes in the hemodynamic functions (cardiac output, circulating blood volume, arterial blood pressure, and cyanide circulation time) during the first week following coronary occlusion.

METHODS

Thirty-six dogs were used for the experiments. In twelve of these the stellate and thoracic (1 to 6) ganglia were removed on both sides in stages (generally within one month). In 24 dogs the ganglia were left intact. These, therefore, served as controls. After recovery from the ganglionectomy, acute occlusion of the left anterior descending coronary branch close to its origin was performed in all dogs by dissection and ligature.

Hemodynamic studies were carried out according to the methods employed by Gross, Mendlowitz, and Schauer.[3] These tests were performed under nembutal anesthesia immediately before ligation of the vessel, one-half hour after ligation, twenty-four hours later and one week later. Ten of the control dogs were from a series previously reported.[3] The remaining control dogs were studied simultaneously with ganglionectomized ones.

One week after the ligation of the left anterior descending coronary branch, the surviving dogs were sacrificed. The left anterior descending branch was probed to ascertain the occlusion, and the size of the infarct was determined by measuring the longitudinal and transverse diameter of the surface of the infarcted area. In order to determine how deep the infarction extended into the myocardium, the coronary vessels were injected under standard conditions with a barium sulfate suspension in gelatine according to the method described by Gross.[6] Roentgenograms were then made of the whole heart and of serial transverse slices 6 mm. thick.[7, 8]

RESULTS

Of the 12 ganglionectomized dogs, two (16 per cent) died within twenty-four hours after the operation. Six (50 per cent) survived twenty-four hours but died within one week. Four (33 per cent) survived one week and were then sacrificed. The causes of death in the two animals which died within twenty-four hours were heart tamponade due to hemorrhage into the pericardium, and acute cardiac failure, respectively. The causes of death in the remaining animals dying within one week were secondary shock, cardiac failure, and pneumonia. Eliminating from this series those dogs which died from pneumonia or hemorrhage leaves a one-week survival rate of 56 per cent.

Of the 24 control dogs, seven (29 per cent) died of ventricular fibrillation during or immediately after the left anterior descending coronary branch ligation; and 9 additional dogs (37 per cent) died within twenty-four hours after ligation. Five of these dogs had pneumonic patches, one probably died of the effect of cyanide and the rest of cardiac failure. Seven (29 per cent) survived one week and were then sacrificed. Elim-

inating from this series those dogs which died from pneumonia leaves a one-week survival rate of 39 per cent.

The immediate fall in average cardiac output after coronary ligation was of about the same magnitude in both the ganglionectomized (Tables I and II) and control dogs* (approximately 50 per cent of preligation level). After twenty-four hours the average cardiac output approximated preligation values in the control group whereas there was only a small rise in the ganglionectomized dogs (Fig. 1). After one week, the ganglionectomized dogs exhibited a further rise in cardiac output

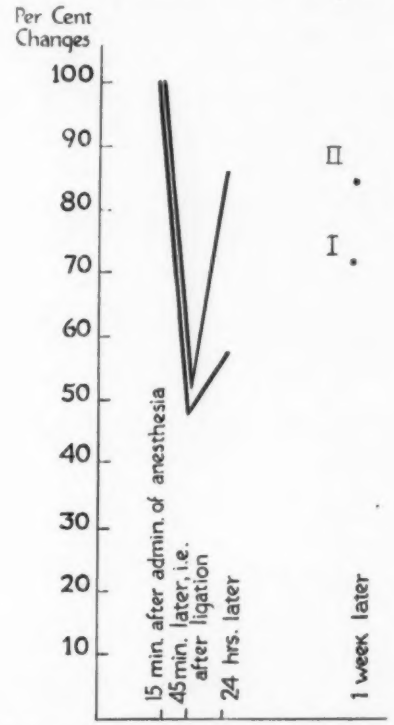

Fig. 1.—Average per cent of changes in cardiac output per square meter of surface area after occlusion of the left anterior descending coronary branch.

I. Ganglionectomized dogs; *II.* Dogs with ganglia intact. This curve represents average values from a group previously reported[3] plus experiments performed simultaneously with the ganglionectomized dogs.

to 72 per cent of the preligation values, and the control dogs showed relatively little change.

In both groups of animals (Table II), coronary ligation was followed by an immediate moderate fall in arterial blood pressure which reached 62 per cent of the preligation level at the end of twenty-four hours. One week after the coronary ligation there was an appreciable rise in the ganglionectomized group, but the blood pressure in the control group

*For detailed data on hemodynamic changes in control dogs, see reference 3.

TABLE I

HEMODYNAMICS FOLLOWING LEFT ANTERIOR DESCENDING CORONARY BRANCH LIGATION IN STELLATE GANGLIONECTOMIZED DOGS

DOG NO.	SEX	PROCEDURE	DATE	WEIGHT IN KG.	PULSE PER MIN.	CARDIAC OUTPUT			BLOOD VOLUME PER SQ. METER IN C.C.	MEAN ARTERIAL BLOOD PRESSURE IN MM. MERCURY	CYANIDE CIRCULATION TIME IN SEC.	DATE OF DEATH	SURFACE MEASUREMENTS OF INFARCT
						OXYGEN CONSUMPTION IN C.C. PER MIN.	ARTERIO-VENOUS OXYGEN DIFF. IN VOLUME PER CENT	MINUTE VOLUME PER SQ. METER IN C.C.					
92	♂	Preligation	12/15/36	8.0	120	91	1.39	14580	2533	120	8	12/17/36	3 × 4 cm.
		Postligation		8.0	112	66	3.53	4175	–	85	13		
		Retested	12/16/36	7.7	112	84	3.42	5640	1734	30	–		
93	♂	Preligation	12/16/36	8.5	100	80	1.95	8820	2198	118	14	12/17/36	1.5 × 2 cm.
		Postligation		8.5	112	68	7.01	2090	1300	75	25		
		Retested	12/17/36	8.2	128	77	6.18	2748	1495	72	30		
17	♂	Preligation	12/17/36	11.7	100	121	2.97	7048	2326	128	11	12/24/36	5 × 4 cm.
		Postligation		11.7	92	106.5	4.73	3897	2483	100	16		
		Retested	12/18/36	11.0	116	110.5	4.39	4538	2352	85	17		
		Retested	12/24/36	9.8	108	98	5.31	3598	2285	95	indefinite		
54	♂	Preligation	12/22/36	10.5	118	107	3.88	5110	2072	123	10	12/29/36	4 × 3.5 cm.
		Postligation		10.5	108	93.5	5.55	3120	1928	100	13		
		Retested	12/23/36	10.4	114	97	4.79	3783	1852	85	19		
		Retested	12/29/36	10.4	108	93	4.08	4250	–	110	–		
80	♂	Preligation	12/28/36	11.4	130	101	2.12	8365	2200	168	10	12/31/36	2 × 2 cm.
		Postligation		11.4	104	85	2.91	5113	1636	125	11		
		Retested	12/29/36	11.0	106	110	2.88	6880	2118	125	7		

TABLE I—CONT'D

29	♀	Preligation	1/26/37	9.2	92	90	6.35	2882	2098	115	13	2/ 1/37	4 × 3.5 cm.
		Postligation		9.2	72	71	6.28	2300	1933	65	35		
		Retested	1/27/37	8.6	140	85	5.72	3158	2120	65	15		
30	♀	Preligation	1/28/37	16.3	108	148	1.79	11370	2546	130	10.5	2/ 1/37	5 × 4 cm.
		Postligation		16.3	124	165	6.48	3525	2610	112	22.5		
		Retested	1/29/37	15.7	112	146	7.42	2803	2598	85	35.0		
44	♂	Preligation	1/29/37	18.2	120	149	3.15	6124	2307	128	9	2/ 5/37	3 × 2 cm.
		Postligation		18.2	128	130	6.47	2598	2108	98	20.5		
		Retested	1/30/37	17.8	120	134	6.80	2585	2096	70	24		
		Retested	2/ 5/37	17.5	112	135	5.05	3532	-	75	18		
64	♂	Preligation	2/ 2/37	10.0	100	87	3.59	4648	2442	105	14	2/10/37	5 × 3.5 cm.
		Postligation		10.0	84	76	4.89	2980	2198	65	37		
		Retested	2/ 3/37	9.6	84	94	6.43	2883	2980	65	25		
		Retested	2/10/37	10.3	104	99	4.15	4480	2548	112	10.5		
82	♂	Preligation	2/ 3/37	9.3	100	169	2.25	15160	-	105	11	2/ 3/37	No infarct
		Postligation		9.3	100	154	6.70	4630	-	90	-		
81	♂	Preligation	2/ 9/37	13.6	102	111	2.48	7000	1796	158	9	2/13/37	4.5 × 4 cm.
		Postligation		13.6	86	103	4.00	4020	1736	105	12		
		Retested	2/10/37	12.9	108	115	6.26	2988	1473	90	indefinite		
96	♀	Preligation	2/15/37	11.0	124	97	2.06	8483	1936	85	12	2/16/37	4 × 3 cm.
		Postligation		11.0	104	88	4.15	3820	1494	88	19		

remained at approximately the same level as that at the end of the twenty-four-hour postligation period.

Following coronary occlusion (Table II) the cyanide circulation time was immediately increased in both groups. The delay was somewhat greater in the ganglionectomized animals. The changes persisted for at least twenty-four hours and reached almost normal values at the end of one week.

The circulating blood volume (Table II) showed an insignificant drop in both groups, with rapid restoration to preligation levels. The hemoglobin determination presented no significant deviations from the preligation levels in either group. The temperature showed a slight drop in both groups after ligation. The pulse became irregular im-

TABLE II

COMPARISON OF THE AVERAGE HEMODYNAMIC CHANGES DUE TO CORONARY LIGATION IN STELLATE GANGLIONECTOMIZED DOGS AND IN DOGS WITH INTACT STELLATE GANGLIA

	PRELIGATION	POST-LIGATION	24 HR. LATER	1 WK. LATER
Cardiac output*				
Ganglionectomized	100	48.4	57.2	72.1
Controls	100	51.9	85.8	84.1
Blood volume*				
Ganglionectomized	100	88	92	101
Controls	100	94	102	102
Arterial blood pressure†				
Ganglionectomized	100	74	62	79
Controls	100	84	62	65
Cyanide circulation time†				
Ganglionectomized	100	186	195	129
Controls	100	166	169	123

*Average per cent changes per square meter of surface area.
†Average per cent changes.

mediately after the ligation in most of the controls but in none of the ganglionectomized animals. Some of the latter showed an irregular pulse only after twenty-four hours.

In judging the extent of infarction, it should be borne in mind that it is unsafe to draw conclusions from the surface measurements alone. Injection of infarcted hearts with barium sulfate gelatine under standard conditions with subsequent radiography and study of serial cross-sections discloses that infarcts which show a small surface area may at times present extensive involvement of the interventricular septum. Furthermore, in appraising the comparative extent of the infarction, differences in the weight of the dogs must also be considered. Based on these criteria there did not appear to be an appreciable difference in the size of the infarcts between the ganglionectomized dogs and those with intact ganglia.

DISCUSSION

Our observations as to the immediate onset of ventricular fibrillation, as well as the mortality rate within the first twenty-four hours after coronary branch ligation, confirm the findings of Cox and Robertson in that these appear to be significantly lower in the ganglionectomized animals. Furthermore, survival one week after vascular ligation appeared to be higher in the ganglionectomized dogs. Unfortunately, the total number of animals studied was too small to warrant definite conclusions as to ultimate survival rate.

With the reservations mentioned above, there did not appear to be an appreciable difference between the two groups as regards the size of the infarct. It is noteworthy in this connection that Cox and Robertson studied the size of the infarcts several months after coronary occlusion. Because of the considerable variability in the rate of cicatrization of infarcts we feel that their results in this connection cannot be accepted without reserve, especially since no injection studies were made.

The only significant hemodynamic changes which followed coronary occlusion were decrease in cardiac output, delay in cyanide circulation time, and fall in mean arterial blood pressure. The immediate changes were of about the same degree in both groups of animals. Within a week following the vascular occlusion the cyanide circulation time had almost reached preligation levels in both groups of animals. The controls showed a considerable return to normal in cardiac output within twenty-four hours after coronary ligation, whereas the ganglionectomized group showed a somewhat slower return to normal values. On the other hand, the ganglionectomized group showed a somewhat better restoration of mean arterial blood pressure at the end of one week. Although the number of animals which survived one week was small, it would appear that, with the possible exception of the mean arterial blood pressure, within one week after vascular ligation these hemodynamic functions were not significantly different in both groups of animals.

SUMMARY

Studies on mortality rate, cardiac output, pulse rate, arterial blood pressure, cyanide circulation time, and blood volume as well as measurement of the size of the infarcts following occlusion of the left anterior descending coronary branch were carried out in dogs with stellate ganglia intact and in stellate ganglionectomized dogs. These studies were done immediately before vascular ligation, immediately after ligation, twenty-four hours, and one week after ligation. Following occlusion of the left anterior descending coronary branch there occurred in both groups of animals a fall in cardiac output, delay in cyanide circulation time, and fall in blood pressure. It is shown that these hemodynamic changes tend to return to normal values after one week.

The other hemodynamic functions studied showed no appreciable changes. The incidence of ventricular fibrillation and the immediate mortality rate was lower in the ganglionectomized dogs. The size of the infarcts was not appreciably different from the controls.

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ELECTROCARDIOGRAPHIC CHANGES IN THE DOG FOLLOWING SUDDEN OCCLUSION OF THE LEFT ANTERIOR DESCENDING CORONARY BRANCH UNDER VARIOUS EXPERIMENTAL CONDITIONS*

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MANY reports have appeared on the electrocardiographic changes following ligation of the anterior descending branch of the left coronary artery in dogs. The authors, however, are not agreed on the characteristic findings. Following left anterior descending coronary branch ligation on 11 dogs, Smith[1] found that the T-waves were first exaggerated, became negative in twenty-four hours, gradually came back to normal and then remained isoelectric or negative. Otto[2] studied only Lead II following this procedure. He described an abnormally depressed R-T segment and a high peak of the T-waves. Feil, Katz, Moore, and Scott[3] found no changes in the R-T segment of the electrocardiogram following ligation of the left anterior descending coronary branch unless the blood supply to the heart was impaired by occluding the inferior vena cava for five minutes. Barnes and Mann[4] observed that occlusion of branches of the left coronary artery produced an elevation of R-T_1, depression of S-T_3, and marked negativity of T_1. Kountz and Hammouda[5] produced occlusion of the anterior descending branch of the left coronary artery in heart-lung preparations in dogs. Their most frequent findings were elevation of the R-T segment in all three leads, and an occasional depression of R-T_1 and S-T_3. The T-waves were usually inverted in all three leads but occasionally inverted in Lead I and upright in Lead III. Harris, Sutherland, Ramsey, and Gaiser[6] found no constant changes following left anterior descending branch occlusion in 17 dogs. R-T_1 elevations were noted only four times. In an admirably painstaking and thorough study of serial electrocardiograms in 51 dogs taken before and after ligation of the left anterior descending branch, Harris and Hussey[7] concluded that this procedure is followed by regular changes, namely, early R-T deviation of the T_1 type (78 per cent of cases), increased amplitude of the T-waves and sharp negativity of the T-waves, particularly in Lead I. Disturbances in rhythm followed a definite pattern progressing through the following stages: (1) ectopic beats singly or from multiple foci; (2) paroxysms

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of ectopic ventricular tachycardia; (3) ventricular flutter; (4) ventricular fibrillation. In some dogs which survived these changes, this sequence was reversed. Harris and Hussey noted further the extreme variability of the normal T-waves in dogs, sometimes finding negative T-waves even in all three leads in the control tracings. This confirms the observations of Katz and his associates[8] who believed these changes were due to the mobility of the heart in the dog's chest.

In a series of experimental studies on partial and complete coronary sinus obturation followed by sudden occlusion of the left anterior descending coronary branch carried out by Gross and collaborators,[9-12] an opportunity was afforded to determine the electrocardiographic changes due to a variety of experimental procedures. Those following coronary sinus obturation have already been reported elsewhere.[10] The present report deals with the electrocardiographic findings in the following groups of animals:

A. Thirty-four dogs in which only left anterior descending coronary branch occlusion was performed:
   1. By dissection and ligation of the left anterior descending coronary branch in the open chest (10 dogs).
   2. By ligation without dissection of the left anterior descending coronary branch in the open chest (15 dogs).
   3. By the double carrick-bend knot method[11] in the closed chest (9 dogs).

B. Thirty-five dogs in which left anterior descending coronary branch occlusion was performed in the open chest by ligation, after recovery from an initial preparatory operation consisting of:
   1. Complete obturation of the coronary sinus (7 dogs).
   2. Partial obturation of the coronary sinus (21 dogs).
   3. Manipulation of the coronary sinus ostium (7 dogs).

C. Twenty-four control dogs in which the left anterior descending coronary branch was either:
   1. Dissected without subsequent occlusion (7 dogs), or
   2. Dissected and loosely surrounded by a double carrick-bend knot (17 dogs).

All operative procedures, including vascular occlusion by the double carrick-bend knot method, were carried out under intravenous nembutal anesthesia. The dissection or ligation of the left anterior descending coronary branch was performed approximately 2 cm. below the ostium of the left coronary artery. The observations made during the course of these experiments will be discussed under two headings, viz.:

I. Summary of the electrocardiographic changes following left anterior descending branch occlusion under the conditions listed in Groups A and B; and the findings in Group C, in which the coronary branch was manipulated but no occlusion was produced.

II. Differences noted in the several groups and subgroups.

I. SUMMARY OF ELECTROCARDIOGRAPHIC CHANGES FOLLOWING SUDDEN COMPLETE OCCLUSION OF THE LEFT ANTERIOR DESCENDING CORONARY BRANCH UNDER THE CONDITIONS LISTED IN GROUPS A, B, AND C

Sudden complete occlusion of this vessel was obtained in 69 dogs. Electrocardiograms were taken pre-operatively, during anesthesia with the pericardium opened, after manipulation or dissection of the left anterior descending branch, immediately after occluding the vessel, and at various intervals (one to three days) after the operation until the dog died or was sacrificed. Because of the low voltage in Lead I in dogs, it was found advantageous to take records of this lead by using a standardization twice that of the conventional one (1 millivolt equals 2 cm.), as well as the conventional Lead I.

R-T Changes

The electrocardiographic findings most characteristic in dogs after ligation of the left anterior descending branch, appeared in the R-T and S-T segments (Table I). In most cases the changes consisted of R-T_1

TABLE I

PER CENT OF DOGS SHOWING R-T_1 ELEVATION AND S-T_2, AND S-T_3 DEPRESSION FOLLOWING THE VARIOUS PROCEDURES LISTED

		PROCEDURE		R-T_1 ELEVATION	S-T_2 DEPRESSION	S-T_3 DEPRESSION	R-T_1 ELEVATION OR S-T_3 DEPRESSION
SUDDEN COMPLETE LEFT ANTERIOR DESCENDING BRANCH OCCLUSION	A. Unprepared dogs*	1. Dissection and ligation	(10 dogs)	70	40	60	80
		2. Ligation	(15 dogs)	46	53	53	80
		3. Double carrick-bend knot ligation	(9 dogs)	88	33	54	88
		Total unprepared dogs	(34 dogs)	65	44	53	82
	B. Prepared dogs†	1. Complete coronary sinus occlusion	(7 dogs)	86	57	57	86
		2. Partial coronary sinus occlusion	(21 dogs)	81	61	71	95
		3. Manipulation of coronary sinus ostium without occlusion	(7 dogs)	71	44	44	85
		Total prepared dogs	(35 dogs)	80	57	62	91
	A. + B.	TOTAL PREPARED AND UNPREPARED DOGS	(69 dogs)	72	50	58	90
CONTROL SERIES (No left anterior descending branch occlusion)	C.	1. Dissection only	(7 dogs)	0	14	14	14
		2. Loose double-carrick-bend knot	(17 dogs)	0	11	11	11
		Total controls	(24 dogs)	0	12	12	12

*No preliminary coronary sinus occlusion.

†Ligation of the left anterior descending coronary branch was performed in these animals after recovery from the procedures listed.

elevations or S-T_2 and S-T_3 depressions. One or both of these changes occurred in 90 per cent of the ligated dogs, usually within fifteen minutes after the occlusion, and tended to disappear within or shortly after twenty-four hours. The R-T_1 segment was elevated in 72 per cent of dogs with occlusion, whereas this never occurred in the control dogs. S-T_3 depression was found in 58 per cent of the ligated animals and in only 12 per cent of the control dogs. As a rule, when the deviations were present in the control groups, they were not as marked as in those with ligation.

Rhythm Changes

On rare occasions, single and infrequent ventricular premature beats followed the administration of anesthesia. After left anterior descending branch occlusions, these premature contractions became very much more frequent. They apparently originated from the left or right ventricles and from one or more foci in each ventricle. They occurred either singly or in short or long paroxysms, and merged imperceptibly with what was interpreted as ventricular extrasystolic tachycardia, or ventricular anarchy. In the latter instances, P-waves were usually observed and were of regular rhythm. This type of ventricular rhythm was noted only once in control dogs and ten times in dogs following coronary occlusion. There is no doubt but that abnormalities in rhythm occur very much more frequently than noted by us electrocardiographically. We have observed them before electrocardiograms could be taken, the hearts resuming normal rhythm or, on the other hand, changing to ventricular fibrillation. The changes were very rapid and sometimes transient. In one instance, immediately after occluding the left anterior descending branch from outside the chest (double-carrick-bend knot), Lead I showed typical R-T_1 elevation with regular sinus rhythm, while Lead II showed ventricular fibrillation. It is estimated that these changes occurred in less than five seconds. No instance of auricular premature contraction or auricular fibrillation was observed.

Other Changes

The QRS voltage did not vary uniformly in either the control or ligated dogs. Opening the chest and instituting artificial respiration produced QRS voltage variations synchronous with the respiratory phases. Alternation of the QRS complex was noted only once in the control series. This dog was apparently in surgical shock. Slurring and notching occurred as frequently in control dogs as in the ligated ones. When the rhythm was regular, the duration of the QRS deflection varied within normal limits and inversely with the heart rate.

Because of the normal variation of T-waves in dogs occurring from day to day, only those records taken before and immediately after a given procedure were compared. The normally low or iso-electric T_1

tended to become inverted though still low in amplitude after left anterior descending branch ligation. T_2 and T_3, on the other hand, tended to become more positive, i.e., the upright T-wave became greater in amplitude and the inverted T-wave became smaller in amplitude after such ligation. One cannot say with certainty whether these changes are characteristic of left anterior descending branch occlusion in dogs. They occurred in 21 per cent of the control animals and in 67 per cent of the animals in which the coronary branch had been occluded. Very similar changes were reported by Gross, Silverman, and Master[10] following coronary sinus occlusion in dogs. Right ventricular preponderance was observed in five ligated dogs but in none of the controls.

II. DIFFERENCES IN THE ELECTROCARDIOGRAPHIC FINDINGS DUE TO THE VARIOUS PROCEDURES LISTED ABOVE

In order to observe whether occlusion of the left anterior descending branch within a closed chest wall was followed by changes which differed from such occlusion performed in the usual manner (open chest), the double carrick-bend procedure was employed. This was performed by placing two loose ligatures around the coronary artery and leading the ends through the pericardium and chest wall.[11] The ligatures were so arranged that tension applied to them after the chest wall was completely closed and healed produced an immediate and complete occlusion of the coronary branch. This occlusion was performed in the anesthetized animal about one week after recovery from the initial operation. The somewhat greater frequency of $R\text{-}T_1$ elevations following this procedure than those following ligation or ligation plus dissection in the open chest (Table I), may be due to improved technique.

$R\text{-}T_1$ elevations appear to be somewhat more frequent in the groups in which previous coronary sinus obturation preceded coronary artery occlusion (Table I). These changes may possibly be attributable to congestion of the heart producing axis deviation, or to added damage to the myocardium due to congestion, or to both.

Table II lists the combinations of $R\text{-}T_1$ $S\text{-}T_2$ and $S\text{-}T_3$ deviations following various procedures. The groups are too small to warrant definite conclusions but are listed as a matter of record.

SUMMARY AND CONCLUSIONS

The reported groups of experiments confirm the findings of Harris and Hussey.[7]

Sudden complete occlusion of the anterior descending branch of the left coronary artery in the dog is followed characteristically by an upward deviation of the R-T segment of the electrocardiogram in Lead I, and a downward deviation from the iso-electric level in Leads II and III. Either or both of these changes were noted in 90 per cent of ligated dogs as compared with 12 per cent in the control dogs.

TABLE II

PER CENT OF DOGS SHOWING CERTAIN COMBINATIONS OF R-T_1, S-T_2, AND S-T_3 DEVIATIONS DUE TO THE VARIOUS PROCEDURES LISTED

SUDDEN COMPLETE LEFT ANTERIOR DESCENDING BRANCH OCCLUSION											CONTROL SERIES		
Unprepared dogs*							Prepared dogs†				(No left anterior descending branch occlusion)		
R-T_1	S-T_2	S-T_3	Double carrick-bend ligation (9 dogs)	Ligation (15 dogs)	Dissection and ligation (10 dogs)	Total (34 dogs)	Complete coronary sinus occlusion (7 dogs)	Partial coronary sinus occlusion (21 dogs)	Manipulation of coronary sinus ostium without occlusion (7 dogs)	Total (35 dogs)	Dissection only (7 dogs)	Loose double carrick-bend knot (17 dogs)	Total (24 dogs)
↑	↓	↓	34	20	30	25	57	52	29	48			
↑	0	0	22		20	11	29	24	43	28			
0	↓	↓		20	10	11		9	14	8	14	11	12
0	0	0	11	13	20	14	14	5	14	8	58	89	80
0	0	↓				0		5		3			
↑	0	↓	22		10	8		5		3			
↑	↑	↑	11	13		8							
0	↑	↑		34		14					14		4
↑	↑	↓			10	2							
↓	0	0									14		4

*No preliminary coronary sinus occlusion.

†Ligation of the left anterior descending coronary branch was performed in these animals after recovery from the procedures listed.

These changes are comparable to electrocardiographic findings in the human being following anterior infarctions. Unlike the latter, however, the R-T segment tended to return to normal very early. This may be due to the fact that the dogs had no coronary sclerosis or myocardial fibrosis and were therefore capable of compensating more rapidly for the sudden change in the myocardial physiological functions.

The characteristic cove-plane inversion of the T-waves in humans was noted in normal dog electrocardiograms. However, comparing records before and after left anterior descending coronary branch occlusion showed a tendency for T_1 to become more inverted and for T_2 and T_3 to become more upright.

Rhythm abnormalities ranging from single ectopic beats to ventricular fibrillation were noted with great frequency following sudden complete coronary occlusion.

In an attempt to increase the blood supply to the heart and thus diminish the incidence or size of infarction, partial and complete coronary sinus obturation was performed in a number of the dogs prior to the coronary branch occlusion. In the comparatively few animals in which electrocardiographic studies were made there was found a slightly greater incidence of changes considered characteristic of coronary occlusion, but there was no definite correlation between the size of infarct and the degree of electrocardiographic changes.

Other differences in the electrocardiographic findings due to various procedures are discussed and listed.

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INFARCTION OF THE HEART

A Morphological and Clinical Appraisal of Three Hundred Cases*

Part I. Predisposing and Precipitating Conditions

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THE basis of this study consists of 300 autopsied cases selected from 9,626 consecutive protocols in the department of pathology of this hospital for the years 1906 through 1936.† Selection was determined by the finding of (1) typical morphological infarction with or without complete obstruction of the nutrient artery; (2) well-defined gross scar 2.5 cm. or more in diameter, with or without complete occlusion of the artery; (3) embolic or other apparently sudden occlusion without gross damage, but with early microscopic change. No cases are included in which death came at once; all survived at least one hour. At least 11 cases of complete occlusion (2 syphilitic, 1 embolic and 8 arteriosclerotic) were discarded because evidence of resultant damage was equivocal. Cases incompletely or vaguely described as myelomalacia cordia, fatty degeneration, myocarditis or senile degeneration were omitted.

After the cases were selected the clinical records were examined. A few clinical records were incomplete so that data on some of the factors analyzed were lacking. In the text and tables the percentages are given on the basis of the number of cases in which the factors in question were ascertained, rather than on the whole group.

During the thirty-one-year period covered by the study there were 697,099 admissions to the hospital, 58,081 deaths and 9,626 autopsies, including the 300 cases presented. Since post-mortem examinations in this country average 1 or 2 per cent of all deaths, in contrast to 17 per cent for the group here, the possible statistical error is considerable in such a study as this. The percentage of autopsies obtained is largely influenced by interest of the permission seeker, which in recent years has been great in cases of suspected coronary thrombosis. Many other factors also preclude accuracy in drawing statistical conclusions.

Arteriosclerosis and Myocardial Infarction

The overwhelming majority of all cases of myocardial infarction are due to coronary arteriosclerotic changes, which may or may not result

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†These have been compiled under the direction of Dr. Frank B. Mallory and Dr. Frederic Parker, Jr., and include gross and microscopic studies by the junior and senior pathologists.

in thrombosis. The term coronary occlusion has become tantamount to cardiac infarction, a synonymy not altogether justified. Arteriosclerosis, and especially atherosclerosis, is usually associated with old age, though an early variety has been reported in infants[19] and in young adults.[47, 20] In a combined necropsy and experimental study Leary has called attention to two fundamentally different types of arterial change evoked by the pathogenesis in old and in young animals or human beings.[23, 24] The young react with a fibrotic lesion which predominates over the lipoid deposits. Later subendothelial necrosis extends to the endothelium, and finally narrowing and thrombosis result. In the older group the lesion is characterized by the accumulation of lipoid cells with but minimal fibrous tissue support, finally causing thrombosis by rupture of the atheromatous abscess.

The work on experimentally produced arterial disease has been immense.[10] It seems that sclerosis may be produced by injections of epinephrine or of bacteria, or by high protein diets.[37] Atherosclerosis can be induced in rabbits by high cholesterol feedings. There are contributory factors of stress, toxicity, and inflammatory localization. Leary believes that when hypercholesteremia occurs in conjunction with (or perhaps as a manifestation of) a disturbed cholesterol metabolism, atherosclerosis will occur. He cites the experience of Joslin and Rabinowich, who have noted a decrease in juvenile arterial lesions since the high fat diet was abandoned in treatment of diabetes. Freyberg and his coworkers[14] think lack of regulation of the diabetic state rather than a diet high in fat causes hypercholesteremia. Levy[30] has called attention to an unusually high incidence of coronary sclerosis in glomerulonephritis and hypothyroidism as well as diabetes mellitus.

In this series generalized arteriosclerosis as manifested by the necropsy evidence, particularly of a diseased aorta, or by the clinical findings of thickened, tortuous, or calcified vessels, or arteriosclerotic changes in the retinal arteries, was present in 261 of 272 in whom data were found. In 8 it was extreme, in 18 slight or minimal, and in the rest it was moderate. Coronary occlusion is usually associated with coronary sclerosis, but generalized arteriosclerosis is not necessarily present. Peripheral sclerosis is often of the medial type,[3] whereas in the coronary arteries subintimal change is important. The occurrence of the various types of arteriosclerosis is found in Table I. The preponderance of cases with coronary arterial disease in this series shows its importance in thrombosis and designates it as the prepotent etiological factor.

ADDITIONAL EVIDENCE OF ARTERIAL DISEASE

Cerebral Vascular Disease.—Many other conditions have their origin in arterial changes similar to those occurring in the arteries to the heart,

giving further evidence of disseminated arterial disease. There were 11 instances of hemiplegia which definitely preceded cardiac infarction, and an additional 10 in which it was probable that cerebral injury depended on a local fault but in which embolus could not be ruled out.

Peripheral Arterial Disease.—Nine individuals had suffered from either classical intermittent claudication or disability from pain upon walking. Post-mortem examinations of the leg arteries were not made so it is not certain whether arteriosclerotic or inflammatory lesions were present. Lemann[25] was one of the first to note intermittent claudication and coronary thrombosis in the same individual.[26, 42] Four cases of this series were admitted with arteriosclerotic gangrene, and two with diabetic gangrene not embolic in origin. Two individuals had had amputations for gangrene prior to admission. There was one case of severe frostbite.

TABLE I

THE OCCURRENCE OF VARIOUS TYPES OF ARTERIOSCLEROSIS

TYPE	INCIDENCE	PER CENT
Generalized arteriosclerosis	261 of 272	96.0
Coronary arteriosclerosis	269 of 274	98.2
Peripheral arteriosclerosis (without coronary)	3	
Coronary arteriosclerosis (without peripheral)	8	
No arteriosclerosis	2	

Angina Pectoris.—In this series a reliable history regarding angina was found in 125 records. It had been present in 29 individuals in its typical form, and in 13 there was pain with an atypical distribution or radiation before the initial infarction. This incidence of only 33.6 per cent is lower than Levine's,[26] but the discrepancy may be partly dependent on the class of patients and language difficulties encountered in this hospital, or on the likelihood that previously occurring anginal pain, especially if mild, might well have been forgotten in the more urgent agony of acute infarction.

Arterial Hypertension.—The importance of hypertension in angina pectoris and cardiac infarction has been appreciated for a long time. It can be considered etiological only so far as it is related to coronary artery disease. While Wearn[44] found hypertension in only one of 19 cases, Parkinson and Bedford[38] found it in 49 per cent of 100 cases, Conner and Holt[9] report it in 34 per cent of 287 cases, White and Bland[45] in 25 per cent of 200. Levine[26] found preexisting hypertension in 40 per cent of 145 cases, with a disproportionate number of females. The finding of high arterial pressure in this series is tabulated in Table II. Taking those with known previous hypertension and those with systolic tension over 160 or diastolic over 100, 49.3 per cent of the 270 had elevated blood pressure. Thirty-one per cent were female, 69 per

cent male, the same sex ratio as the entire series. All cases with arterial hypertension showed coronary disease except one case of syphilitic narrowing and occlusion of the coronary mouth. On the other hand, numerous cases had arteriosclerosis without hypertension. The percentage of hypertensives and nonhypertensives having initial infarction in different decades is shown in Fig. 1. Of the women with history of hypertension, 41.4 per cent were obese and only 24 per cent of the men were obese, indicating relatively more women than men with obesity in the hypertensive group.

SEX

In every reported statistical work there has been a notable preponderance of males: Wearn,[44] 10 to 9, Parkinson and Bedford,[38] 165 to

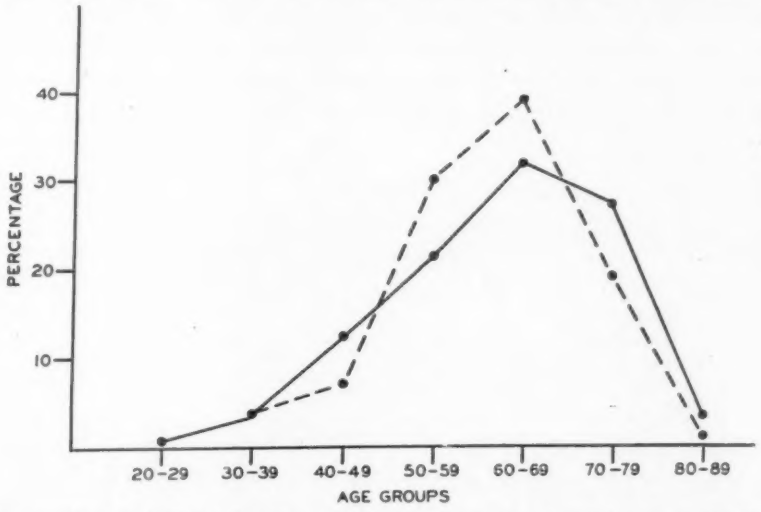

Fig. 1.—Age at initial infarction: Comparison of age at onset among 100 known patients with hypertension (broken line) and 122 cases where hypertension was not demonstrated (solid line).

18, Levine,[26] 111 to 34, Conner and Holt,[9] 244 to 43, White and Bland,[45] 167 to 33, Appelbaum and Nicolson,[1] 125 to 25, Wilhelmy and Helwig,[48] 72 to 16, Goldsmith and Willius,[15] 272 to 28. In these reports taken together the females constituted only 15 per cent of all cases. There were 209 males to 91 females in our group (Table III), or 30.3 per cent females. Thus there was twice the proportion of females in this series as the average in the others. Hypertension was represented proportionally in the two sexes. Though most of the patients in this report died within the last ten years, it is interesting that the sex ratio for the 18 cases in the first ten years was two males to one female, essentially the same as for the total series. There is no indication that the percentage of females dying with myocardial infarction is increasing relative to males, though there are not enough cases in the

TABLE II

PREEXISTING VASCULAR DISEASE AND RELATED STATES

	INCIDENCE	PER CENT
Coronary arteriosclerosis	269 of 274	98.2
Generalized arteriosclerosis	261 of 272	96.0
Hypertension (history and/or elevated blood pressure)	133 of 270	49.3
History positive	66 of 91	72.5
History unknown; blood pressure above 160/100	67	
Angina pectoris		
Typical 29		
Atypical 13	42 of 125	33.6
Diabetes mellitus	19 of 109	17.4
Preexisting hemiplegia		
Definite	11 of 268	4.1
Questionable	10 of 269	3.7
Intermittent claudication	9 of 217	4.1

early periods to be significant. Many causes for male preponderance have been alleged, but none has impressive support. So far, this analysis throws no light on causes of sex difference in incidence, and indicates that probably there has been little change in sex ratio in thirty-one years.

TABLE III

COEXISTING CONDITIONS

	INCIDENCE	PER CENT
Sex		
Males	209 of 300	69.7
Females	91 of 300	30.3
Average age at onset, 61 years (males 60.1; females 61.7)		
Weight		
Obese	67 of 228	29.4
Normal	112 of 228	49.1
Thin	49 of 228	21.5
Gallbladder disease	47 of 269	17.5
Rheumatic valvular disease	14 of 300	4.7
Syphilis		
Serological evidence	23 of 233	10.0
History, serology, and anatomical	33 of 300	11.0
Miscellaneous		
Active tuberculosis	4 of 300	1.3
Peptic ulcer	10 of 300	3.3
Hemochromatosis	1 of 300	0.3
Hodgkin's disease	1 of 300	0.3
Leucemia	1 of 300	0.3

AGE

The age at onset of first infarction could be determined in 222 of the cases presented (see Fig. 2 for percentage distributions). The average age at onset for the whole group was 61, for males 60.1 and for females 61.7 years. The largest incidence in a single decade was in the seventh, in which 35 per cent occurred. Three decades, from 50 to 79, contained 83.7 per cent of the group. The number of cases in the sixth and eighth decades were nearly the same—56 and 52,

respectively. When the incidence of onset in decades is compared on the basis of sex (Fig. 3), it is seen that in the fifth decade there is a slight male preponderance and in the sixth a large one; while in the seventh decade there is a large female preponderance and in the eighth a slight one. Both males and females reach their peak in the seventh

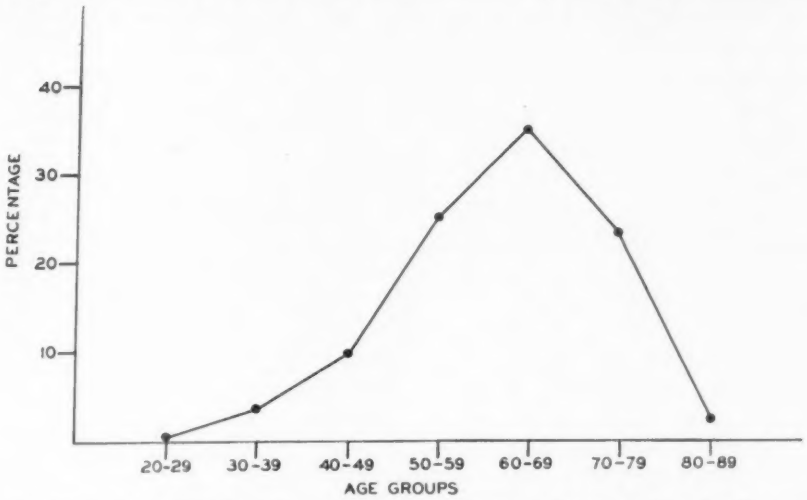

Fig. 2.—Age at initial infarction: Percentage of 222 patients having initial attack in different decades.

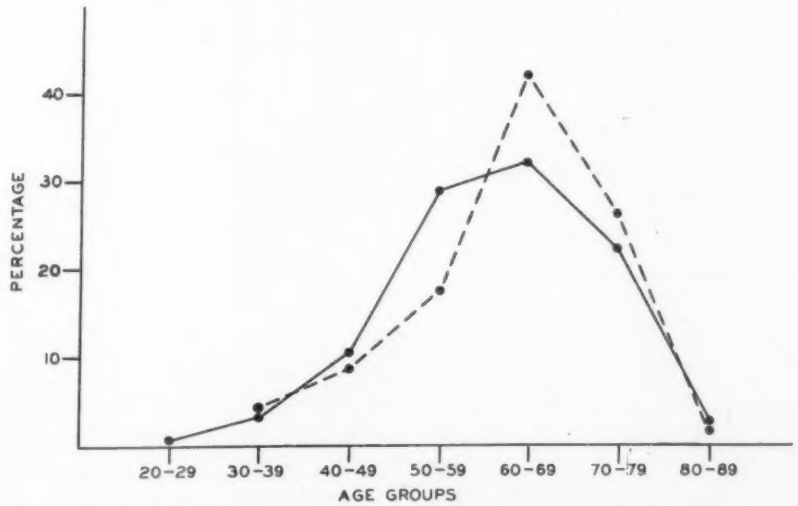

Fig. 3.—Age at initial infarction: Percentages of 153 males (solid line) and 69 females (broken line) in different decades.

decade. Such figures indicate a tendency for the males to have their initial occlusion at an earlier age in the group studied. It is possible that the delay in females is related to the menopause, since the peak in their incidence is two decades after the 40 to 49 decade. It could be correlated, however, with no factor in this analysis. Since the

incidence and severity of coronary disease increase in later decades, age has an important relation to infarction of the heart.

RACE AND COLOR

No record of race is available for hospital admissions over the thirty-one-year period, but several random one-year records show constancy among themselves and also when compared to the whole group. For distribution by race see Table IV. As for color, 283 were white, 16 colored, and 1 yellow. The Russians, definitely more than their proportion in the population, were Hebrews with two exceptions. There were 16 Hebrews. These figures cannot be interpreted as having undue importance, nor race be said to have any unusual rôle in genesis of coronary thrombosis in the cases studied.

TABLE IV

DISTRIBUTION BY RACE

American	168
Irish	31
Colored	16
Canadian	16
Russian	14
English	13
Scottish	6
German	6
Nova Scotian	5
Italian	3
Swedish	3
Lithuanian	2
Syrian	2
Greek	2
Portuguese	2
One case each of French Canadian, Polish, Norwegian, Finn, New Foundlander, Armenian, Japanese, Turk, Latvian, Swiss, Spaniard	11
	300

HEREDITARY FACTORS

Much has been said concerning family tendency to diseases originating in arterial deterioration, and figures of varying impressiveness have been accumulated. The first case report of family tendency in coronary thrombosis was that of Riesman,[41] and a good summary of Musser and Barton[35] appeared in 1931. Goldsmith and Willius[15] obtained positive family history in 55 per cent of their recent series. White[45, 47] has called attention to the family tendency in cases of precocious coronary arteriosclerosis and to the association of moderate, but never marked hypertension, among Hebrews. In many of the present cases no satisfactory history was possible; in a few no relevant data were recorded. Among the 138 cases with satisfactory histories there were 55 instances of family cardiovascular renal disorder, 40 per cent. Nine

instances of apparent coronary thrombosis occurred ("acute indigestion," sudden death below forty-five years) in a parent. In 20, cerebral vascular accidents were known (stroke, "shock," apoplexy). In 14, a parent had died of dropsy or Bright's disease in the arteriosclerotic age period. The hereditary distribution of the 55 cases with positive family history is seen in Fig. 4. Hypertension was present in 70 per cent of this group, but in only 50 per cent of the entire series. Fifty-six per cent had their initial attack before the seventh decade, as compared with 39.2 per cent in the entire group (Fig. 5). From the literature and the data presented it appears that heredity is an important predisposing factor in coronary arteriosclerosis, and that hypertension is related.

BUILD AND WEIGHT

Levine has observed that the thin have less tendency to coronary or general sclerosis than the obese, and this observation is borne out by insurance tables, du Bray,[12] Dublin and Marks.[11] In this series build, or type, was not adequately described in a sufficient number of cases to be conclusive. Exact weight was recorded only in a small proportion. In 228, however, there was enough description of the weight so that an individual fell into the class of (1) obese and overweight, (2) well developed and nourished or (3) thin, emaciated, and undernourished. While this is not a wholly accurate gauge it has value because it is the clinical division into which cases naturally fall and are observed. Sixty-seven, or almost 30 per cent, were obese. Forty-nine, or 21.5 per cent, were thin. One hundred and twelve, or almost one-half, did not deviate from what was considered normal. Comparing the obese in relation to sex, 45 per cent were females and 55 per cent males, whereas only 31.1 per cent of the entire 228 were females —indicating a disproportionate number of females among the obese.

Many patients were thin, some were senile, others had hemiplegia or were physically or economically unable to gain more than fair subsistence. Twelve were victims of chronic disease (tuberculosis, endocarditis, gangrene). The age, sex, and incidence of hypertension of the thin group followed the general pattern. It is manifest that arterial disease is not prevented by thinness, or at least that those with arterial disease may become thin.

There is no available evidence bearing on Levine's belief that the typical patient is well-set, often somewhat overweight, frequently quite strong. In this series obesity occurred more frequently than in normal control groups; was relatively more frequent in women than in men. On the other hand, thinness conferred no immunity. The age at onset among thin, normal, or obese patients did not vary significantly from the group as a whole (Fig. 6). From the inconclusive data heredity does not seem to be necessarily related to body weight in predisposing to infarction.

ASSOCIATED DISEASES

Diabetes Mellitus.—Diabetes mellitus is recognized as a disease of unusual importance in association with arteriosclerosis, and particularly with coronary thrombosis. Nathanson[36] observed coronary sclero-

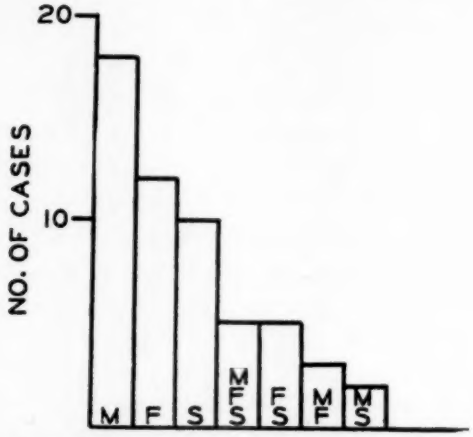

Fig. 4.—Hereditary distribution: Arranged according to the number of patients with involvement of mother, father, or siblings, and combinations. The mother had vascular disease in 28 instances, the father in 25, and siblings in 22 of a total of 55 patients with family vascular disease.

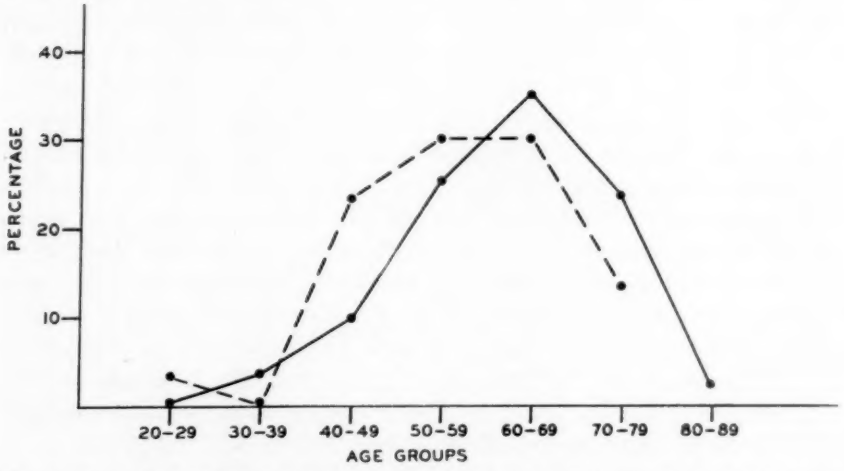

Fig. 5.—Age at initial infarction: Cases with family history (broken line) compared with the entire group of 222 (solid line).

sis in 41 of 100 autopsied diabetic cases. Joslin's figures[21] indicate that recently deaths from coronary disease are higher than those from cerebral or peripheral vascular lesions in diabetics. Insulin, by reducing the deaths from coma and the metabolic mistakes of diabetes, has prolonged life so that more diabetics live to the age when even nondiabetics are prone to develop arteriosclerosis.

Antecedent diabetes occurred in 10 per cent of Conner and Holt's 287 cases,[9] while in Levine's group there were 23.7 per cent with diabetes or transient glycosuria. In this series there were 19 diabetics out of 109 with satisfactory information on this point, 17.4 per cent.

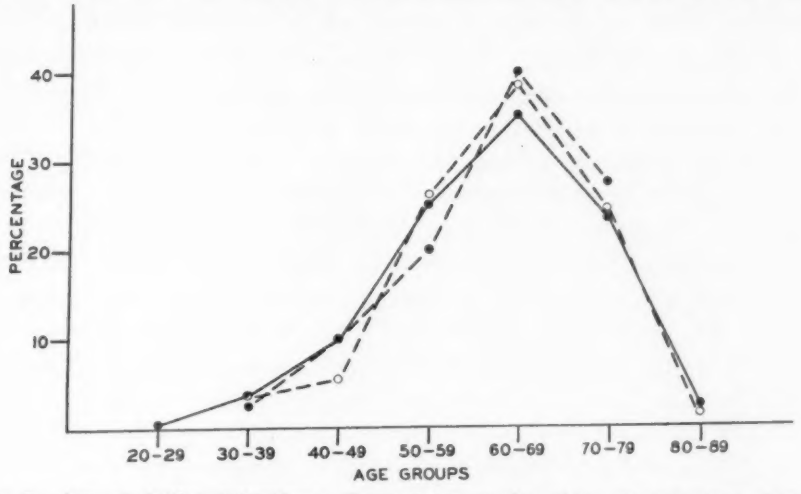

Fig. 6.—Age at initial infarction: Comparison of the obese (broken line—hollow circle), thin (broken line—solid circle), and the entire group (solid line).

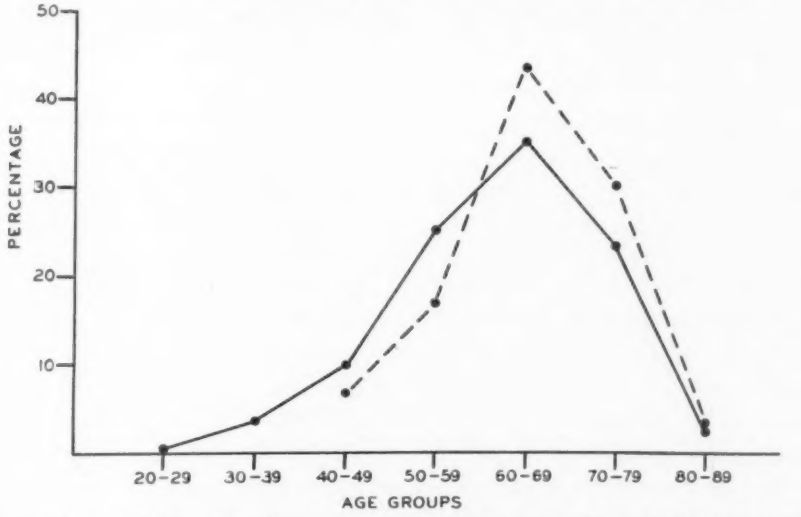

Fig. 7.—Age at initial infarction: Comparison of those with gallbladder disease (broken line) and the entire group (solid line).

Seven of the cases were female, the same proportion as in the whole group. The age at onset averaged one year older than in the general group, with the youngest 35, the oldest 84. Hypertension was present in seven, was not demonstrated in eleven, with no data in three. No instance of freedom of arteriosclerosis, generalized and coronary, was found, though the records are not complete in all cases. In 56 of the

300 patients there is no history on this point and no urine examination, so the incidence in the group may have been higher. Since the only constant finding in these diabetics was arterial disease, it is concluded that diabetes is important in the pathogenesis of coronary thrombosis only so far as it is associated with coronary sclerosis.

Gallbladder Disease.—Although cholecystitis is not primarily a metabolic disease, gallstone, especially of the cholesterol type, probably is secondary to a metabolic disorder,[3, 4] if not a primary fault.[34] Disease of the gallbladder was present in 47, or 17.5 per cent, of 269 patients in which this organ was mentioned. Twenty-one, or 44 per cent, of the cases were in females, a disproportionately large number. There were slight differences from the whole group in the incidence of onset in decades (Fig. 7). Obesity was present in seven, thinness in ten. An absolute correlation was found with arterial disease, since all with gallbladder disease had both general and coronary arteriosclerosis. The latter was extreme in twelve. Stone was present in 90 per cent of those with gallbladder disease, in some cases with little disturbance in the gallbladder structure. It seems probable that the high incidence of gallbladder disease and especially of stone formation is another manifestation, as is obesity, of a derangement of the lipoid-cholesterol metabolism. Stone formation is not of etiological significance in arterial disease, but rather is an expression of a fundamental fault which underlies both processes.

Rheumatic Fever.—Karsner and Bayless,[22] after a review of the extensive literature, maintain that rheumatic fever regularly produces disease in the coronary arteries, inflammatory or fibrotic, or both, and suggest that it predisposes to early coronary sclerosis. The extent of coronary damage in rheumatic heart disease bears a roughly inverse relation to the size of the arteries, being most extensive in the small and less marked in the large ones.[16] The occurrence of rheumatic heart disease in this series is seen in Table V. Since only 3 of 31 instances of initial infarction before 50 were associated with disease, there is no evidence of precocious rheumatic coronary disease in this series, nor is there any indication that rheumatic fever of the type which produces valvular disease is a frequent precursor of coronary sclerosis leading to infarction.

TABLE V

RHEUMATIC VALVULAR DISEASE

History of rheumatic fever and rheumatic lesions	6
No history of rheumatic fever but rheumatic lesions	3
Bacterial endocarditis	5
Total	14
History of rheumatic fever and no rheumatic lesions	13

Syphilis.—Syphilitic heart disease causes narrowing of the mouths of the coronary arteries. This is a recognized cause of cardiac infarction[7] but one that is not necessarily associated with thrombosis. White and Bland[45] found evidence of syphilis in 4 per cent of 200 cases of coronary thrombosis in private practice, Conner and Holt[9] in 14.2 per cent of their cases, Levy[29] in 13.4 per cent, and Parkinson and Bedford[38] in 9.6 per cent of 83 autopsies. Appelbaum and Nicolson,[1] who record an incidence of 6 per cent of 168 autopsies, observe "that modern pathologists do not regard syphilis as an etiological factor in the production of arteriosclerosis." For evidence of syphilis in this series see Table VI. Syphilitic structural changes were contributory to infarction in 8, or 2.7 per cent, of the entire 300 patients.

TABLE VI

SYPHILIS

EVIDENCE	NO. OF CASES	PER CENT
Serology positive	23 (of 233)	10
History positive		
Negative serology (treated)	7	
No serology	1	
Autopsy		
Aortitis (negative serology)	2	
Aortitis (positive serology)	(8)	
Aortitis and aneurysm (positive serology)	(2)	
Total	33 (of 300)	11

ALCOHOL AND TOBACCO

The chronic users of alcohol and of tobacco in this series are tabulated in Table VII. Most of the addicts to either were males. The age at onset in the two groups followed the average quite closely. These figures do not indicate that alcohol and tobacco are regular etiological agents or that use, abuse, or abstinence specifically induces or prevents those lesions which determine coronary thrombosis and myocardial infarction. No light is thrown on White's[46] suggestion that tobacco may induce premature coronary disease in young non-hypertensive Hebrews who lead a sedentary life.

TABLE VII

FACTS OF INTEREST IN HISTORY

HISTORY	INCIDENCE	PER CENT
Family history of vascular disease	55 of 138	40
Use of alcohol		
Excessive	19 of 109	17
Moderate	47 of 109	43
Abstainers	43 of 109	40
Use of tobacco		
Excessive	25 of 89	28
Moderate	35 of 89	39
Abstainers	29 of 89	33

PRECIPITATING CONDITIONS

A degree of tardy prophylaxis against coronary thrombosis might be feasible if the immediate precipitating events were specific and could be avoided or delayed.

Seasonal Variation.—Very striking figures are reported by Wood and Hedley[49] for seasonal variation in onset of coronary thrombosis for three years at Philadelphia in a group of 133 patients. Seasonal variation in death rate has been noted by Bundesen and Falk[6] and by Cohn,[8] as well as in insurance statistics in cardiovascular disease. In this series a considerable monthly variation was found in incidence of acute attacks, with a high of 29 in April and a low of 11 in August. In cases with repeated infarcts, only those subsequent attacks separated by six months or more were included. When the seasonal incidence was observed, using the rough division of December, January, and February as winter, the next three months as spring, and so on, a more striking seasonal variation was found (Figs. 8 and 9). Attention is called to the low incidence of acute coronary occlusion in the summer. Fall, winter, and spring are each represented by high percentages. It is improbable that chance factors, such as hospital admissions or city population shifts in summer, played a large part in these results, as in many cases admission or death followed the onset by weeks, months, or years. The low summer incidence may be correlated with a number of factors, such as increases in temperature, decreases in infections, especially respiratory, or changes in diet. If further substantiation of this seasonal variation is found it may have an important bearing on therapy in arteriosclerotic disease of the coronary arteries.

TABLE VIII

CIRCUMSTANCES AT ONSET

Time of day	
A.M.	28
Noon	1
P.M.	27
Midnight	3
Total	59

RELATION TO EXTERNAL ENVIRONMENT		REST	ACTIVITY	EATING
Sleeping	16	16		
Resting, reclining, awake	13	13		
Sitting quietly	11	11		
Getting out of bed in A.M.	4		4	
Eating	4	4		4
Shortly after eating (some activity)	10		10	10
Moderate exercise	19		19	
Severe exercise	7		7	
Immediately after exercise	4		4	
Totals	88	44	44	14

Time of Day.—Marked changes in cardiovascular activity occur during the phases of daily life with exercise, digestion, emotion, and relaxation. From the data in Table VIII it is clear that time of day

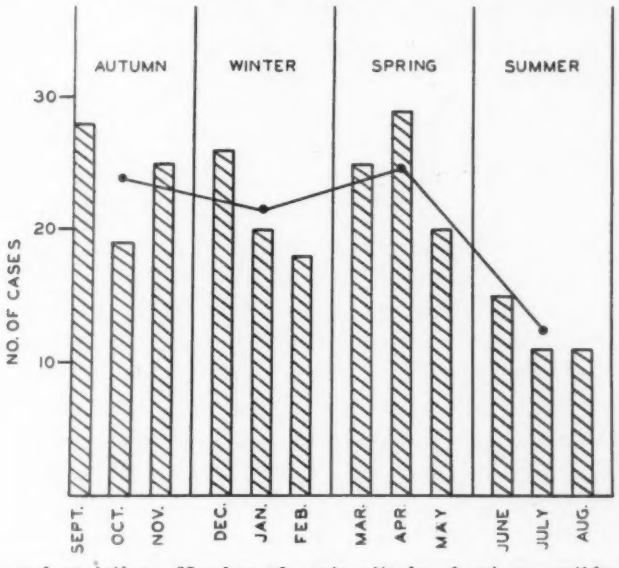

Fig. 8.—Seasonal variation: Number of acute attacks showing monthly distribution and the average for each season (black line) in 247 instances.

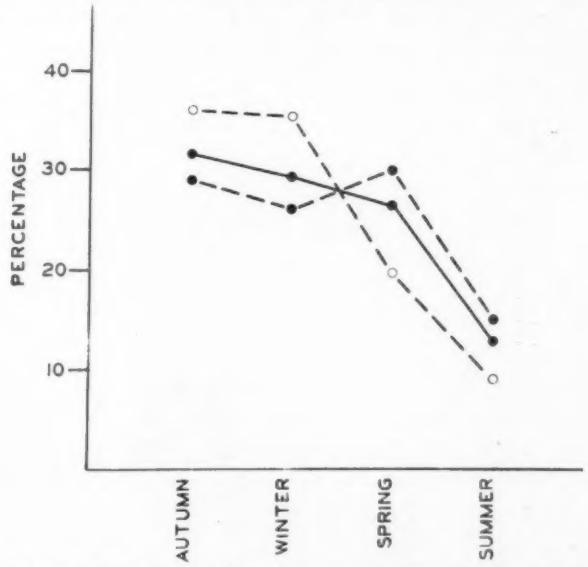

Fig. 9.—Incidence of acute attacks by seasons: Comparison of figures of Wood and Hedley, 133 attacks (broken line—hollow circle), and this series, 247 attacks (broken line—solid circle) and an average of the two series, 380 attacks (solid line—solid circle).

per se was not a factor in this series in determining onset of infarction.

Occupation and Activity.—Most of these patients gave evidence of physical wear and tear. The majority were laborers or housewives,

but analysis by occupational subgroups was not carried out. The state of activity or inactivity in which acute attacks occurred was examined. Belief that thrombosis *usually* occurs during rest[31, 32, 39] is not verified. It appears that no state of existence is safe when the underlying damage is present (Table VIII). There was no difference in precipitating events between those over 50 and those under. Men, by virtue of their daily work, were more frequently active, but women were also overtaken during considerable activity. Altogether in this group occupation or activity did not seem specifically important.

Infection.—Bronchitis was an extremely frequent finding, although no considerable number had bacteriological studies. The finding of bronchitis or bronchopneumonia at autopsy of course does not prove that it was present before the myocardial infarction, except in very recent cases. At least five patients had bronchopneumonia before infarction occurred. In two, empyema antedated infarction; in two chills had occurred before thrombosis; and in two lobar pneumonia was found. Although more careful studies of infection are necessary and no definite conclusion can be drawn, the suspicion is strong that infection may be a precipitating factor in some cases of thrombosis.

Acute Effects of Alcohol and Tobacco.—Four of the 19 chronic alcoholics definitely developed their initial thrombosis while deeply intoxicated. It is probable that two others had the same initiation. In 13 there was no relation. In the 47 moderate drinkers no association was noted. It is concluded that acute alcoholic coma may precipitate occlusion in certain instances where coronary disease already exists. There was no association in any case with the act of smoking, chewing, or using snuff.

Trauma.—Indirect trauma is a known cause of cardiac rupture[43] and has been rarely mentioned as a precipitating factor in occlusion.[17] In three cases in this series it was a possible direct factor. One patient fell from a ladder 8 feet high, striking his chest and fracturing several ribs on the left side. No pain was described before the fall. He suffered severe pain for days. Ten weeks after the fall he died and a fairly recent infarct with early aneurysmal dilatation was discovered. Another fell and hurt his left side in a bath tub, and having suffered undue pain went directly into cardiac failure though there had been neither pain nor failure before. At death, after almost two years, a large myocardial scar was found. In a third case a fall from a ladder resulted in fractured skull. At autopsy, eight days later, old and recent infarcts were found. In the first two cases it is possible that physical violence with changes in intrathoracic pressure and volume, and the reflexes and circulatory disturbances set up by the accident or the shock, may have precipitated thrombosis on the basis of pathological changes which already existed. The rôle of trauma in the third case is not so clear-cut.

Hypoglycemia.—It is recognized that insulin shock may induce coronary thrombosis, as may even sudden reductions of blood sugar without evidence of shock.[2, 13] Probably more than one factor is involved in the mechanism, including peripheral vascular collapse and physiochemical changes in the blood. Insulin was used in all 19 of the diabetics of this series, vigorously in seven. In three it was the most probable precipitating factor in initiating the thrombosis. No case of spontaneous hypoglycemia, such as has been described by Harris (quoted by Harrison[18]), was found in this series. Diabetic coma was associated with one case of thrombosis, but it is not clear which condition appeared first.

Nitroglycerin.—Since 1863, when Lauder Brunton[5] introduced them for relief of angina pectoris, nitrites have been used freely for relief of cardiac pain. With the clinical recognition of coronary thrombosis it was noted that this disease was rarely relieved, and even might be aggravated by the nitrites.[40] In many cases of this series nitroglycerin was used in small amounts (1 to 4 $\frac{1}{100}$-grain tablets), usually with no relief. Two patients took heroic amounts, one 20 tablets, the other 50, over short periods of time before coming to the hospital. If it did not inaugurate it probably did aggravate the condition, since the dilatation, which is necessarily minimal in calcified coronaries, must have been counterbalanced by the disproportionate fall in blood pressure.

Operative Trauma and Shock.—Surgeons, in focusing attention on mistaken diagnoses of acute abdominal conditions where coronary thrombosis exists, have not stressed the danger of operative and anesthetic trauma in inducing thrombosis. Master[33] has recently emphasized the rôle of surgical procedures in inducing infarction, but Levine[28] did not mention it in a study of nine postoperative cardiac disturbances (all arrhythmias)—cases of what had long been called "acute dilatation of the heart." In this series there were eight cases following major operations; in four, the postoperative period was associated with shock, and death resulted from a fresh infarction, while in the remainder the relation was not so clearly established. In one, following a minor procedure (thoracotomy), infarction occurred.

Hemorrhage.—In one case hemorrhage from a peptic ulcer (with vomiting and retching) was followed by shock, for which several transfusions were given. At autopsy a fresh infarct was found. The suspicion of transfusion reaction cannot be eliminated, but hemorrhagic shock seemed to be the precipitating agent. In another, severe epistaxis was followed by markedly reduced hemoglobin and a fresh infarct was found after death. Two others had profound anemia, with hemoglobin below 35, but no certain relation with the coronary thrombosis could be proved.

Miscellaneous.—One patient went into collapse following decompression of the bladder, long distended by chronic prostatic obstruction,

and died with a fresh infarct. In one case with lymphatic leucemia, injection of pentnucleotide was followed by substernal constriction. Nine days later the patient died and a recent infarct was found.

Though in the minds of clinicians the grave form of vascular collapse in cardiac infarction is regularly assumed to be a result, not a cause, of the condition, these cases demonstrate that collapse may be the catalyst in precipitating thrombosis and, continuing, color the clinical picture after infarction has occurred.

TABLE IX

INTERNAL DISTURBANCES

Operative trauma and shock	5
Alcoholic coma	4
Insulin hypoglycemia	3
After trauma to chest	2
After trauma to head?	1
After excessive nitroglycerin	2
Posthemorrhagic shock	2
After bladder decompression	1
Diabetic coma?	1
Transfusion reaction?	(1)
Pentnucleotide reaction?	1
Vascular collapse or related conditions	22

SUMMARY AND CONCLUSIONS

The criteria for selection of 300 cases of infarction of the heart are given and the associated vascular lesions are discussed.

The average age at onset in 222 patients was 61 years, 60.1 for males and 61.7 for females.

Of the entire group of patients, 91, or 30.3 per cent, were females and 209 were males. Proportionately more males had their original attack in the fifth and sixth decades, and more females in the seventh and eighth.

Family tendency to cardiovascular disease was an important factor, appearing in 40 per cent of 138 patients. Seventy per cent of this subgroup had hypertension, whereas only one-half of the entire series had it. The age at onset in those with family tendency was younger than in the rest.

Weight, as judged by division into obese, normal, and thin groups, had no specific effect in predisposing to or protecting from thrombosis. Obesity was abnormally prominent, but thinness also was frequent and conferred no relative immunity.

Diabetes was present in 17.4 per cent of 109 patients, but was not characterized by earlier age of onset. No diabetic was exempt from arteriosclerosis. Gallbladder disease, especially with stone formation, occurred in relatively more females than males, was present in 17.5 per cent of 269 patients, and was always associated with arterio-

sclerosis. Rheumatic heart disease was an unimportant factor in this series. Syphilis, evidence for which was present in 10 per cent of 233 patients, was the direct or facilitating cause of infarction in eight.

The chronic use of alcohol or tobacco could not be regarded as etiologically important. In a few cases alcoholic coma seemed a precipitating factor. The seasonal incidence of onset of infarction was low in the summer months. Time of day, occupation, and activity appeared unrelated to the onset of thrombosis.

Attention is called to the danger of surgical or medical shock as an immediate precursor and precipitating agent in coronary thrombosis when disease already exists in the coronary arteries.

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THE INCIDENCE OF MYOCARDIAL INFARCTION WITHOUT PAIN IN 200 AUTOPSIED CASES*

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IT IS the purpose of this study to determine the incidence of myocardial infarction not associated with pain. At the outset it is necessary to distinguish the symptom designated as pain from other distressing sensations in the chest. The main interest will be centered about those instances in which there was neither pain nor any uncomfortable sensation in the chest. There have been many references in the recent literature to cases of painless coronary thrombosis, but for the most part accurate analyses of other distressing sensations referable to the chest have not been made. In fact it seemed that when an adequate survey of such patients could be made, the occurrence of coronary thrombosis without any of the painful or uncomfortable sensations was by no means as common as had been intimated in recent reports.

In a study based upon 83 cases of coronary thrombosis and cardiac infarction, proved at autopsy, Parkinson and Bedford[13] pointed out that in a certain group of cases pain is not a prominent symptom. The number or frequency of these cases is not given. East, Bain, and Cary[5] reported 8 cases of cardiac infarction with no history of pain. Six of these cases were confirmed at autopsy. Davis[4] in a series of 76 cases found no history of pain in 29, or 38 per cent. Eleven patients who died suddenly were not included in the 29 without pain. Fifty-three of the 76 were confirmed by post-mortem examination. Bruenn, Turner, and Levy[1] found in a series of 33 autopsied cases that after discarding two patients from whom no history was available because they died in coma, 12 (39 per cent) of the remaining 31 had pain with the attack of coronary thrombosis. They found four patients with cardiac aneurysm who had had no pain associated with the final complete occlusion. Katz and his coworkers[14] in a study of 34 cases of coronary thrombosis examined at autopsy found that 13 (38 per cent) of these "did not give any history of cardiac pain." He pointed out, however, that congestive heart failure, debilitating disease or clouded sensorium may explain the absence of pain in a few of these patients but not in the majority.

Other authors have pointed out that myocardial infarctions may occur without pain, but have not indicated their frequency. Wearn,[16] Herrick,[10] Levine and Brown[11] and others[2, 3, 7-9, 12, 15, 17 and 18] have in-

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dicated clearly the occurrence of such cases. Recently there have been many case reports of painless coronary occlusion, most of which have not been proved by post-mortem examination.

The material from which this study was made consisted only of cases of myocardial infarction that were proved by post-mortem examination. The records of the department of pathology of the Peter Bent Brigham Hospital from 1913 to January 1936 were reviewed, and the clinical case histories of every patient receiving a pathological diagnosis of either coronary thrombosis or myocardial infarction were studied critically, and any reference to pain or painful sensation was carefully noted. In most cases the infarct was either the direct cause of death or contributed to it, but in some it was an incidental finding at autopsy and was entirely unrelated to the cause of death. The total number of hearts with such post-mortem diagnoses was 200. Those hearts having infarctions of smaller size than 1 cm. in diameter were not included.

It was found that in some of these cases the clinical history was not satisfactory with regard to establishing clearly whether or not the patient experienced pain. As this point is a crucial one in this study, it was necessary to omit certain cases in order to include only those certainly not associated with pain. For example, it is obviously impossible to establish clearly whether a patient dying suddenly as a result of a myocardial infarction or one having an infarction while in uremic acidosis has experienced pain with the infarction. These and similar cases when omitted are specifically mentioned.

For the purpose of study the cases were divided into two groups according to the age of the infarct. In many instances it was possible to differentiate accurately two or more sites of infarction in the same heart. Counting each of these sites as a separate infarct there was in 200 autopsies a total of 251 separate infarcts which were quite definite. All these infarcts were divided into two groups, according to their approximate age; one consisting of lesions which were of recent origin and showing evidence of acute myocardial damage, the other consisting of lesions of longer duration, with evidence of a healed, fibrous connective tissue scar. The former were all less than eight weeks old and the latter were of much longer duration. Most of the infarcts fell easily into one of these two groups. However, there were several which were in such a state of healing that they had evidence of both fairly recent myocardial damage and of healing in the same area. The gross and, more important, the microscopic appearances of the infarcts in these cases were compared with the appearances of those in which the onsets were known to have occurred not more than six or eight weeks before the time of death. In this way doubtful cases were judged to fall in the old or recent groups. Those cases which had a clear, uncomplicated, clinical history of myocardial infarction were placed in the group of "old" or "recent" cases according to whether the infarction occurred

prior to six to eight weeks before death or not. Those cases having an indefinite onset and those in which the time of onset was not known accurately were placed in the proper group according to the age of the infarct judged by its appearance. According to this arbitrary division there were, in 200 patients, 109 old and 142 recent infarcts. In 51 hearts of this series both old and recent infarcts were found.

The cases of each group were divided according to whether or not the onset of the infarction was associated with pain. It was found that a great many had subjective sensations which were uncomfortable and disagreeable but were not described as painful. A further subdivision, therefore, was necessary to separate those actually having experienced pain from those having less severe sensations which were termed discomfort or distress.

GROUP OF "RECENT" INFARCTS

The total number of recent infarcts was 142. There were 48 cases in this group which had histories unsatisfactory in regard to establishing clearly whether the patient experienced pain at the time of the infarction. In these there were associated or complicating conditions which obscured the onset of the infarction or made it impossible to obtain a satisfactory story from the patient. The cases which were omitted because of unsatisfactory histories were as follows: sudden death 19; uremia 5; deep diabetic acidosis or coma 3; irrational, toxic, stuporous, delirious 9 (these included overwhelming infections of the peritoneum or blood stream, psychoses, and one case of peritonitis from ruptured gallbladder); cerebral embolism or cerebral hemorrhage 5; during or soon after surgical anesthesia and operation 4; during shock from bleeding duodenal ulcer 1; severe cachexia from widespread tuberculosis and amyloid disease 1; case in which heart was brought into pathology department for examination with inadequate history 1.

The 94 remaining cases all had satisfactory histories. The frequency of pain or discomfort is indicated in Table I.

It is apparent that only about 4 per cent of the cases had no pain or distress in the chest and not more than 4 per cent complained merely of discomfort. In fact over 90 per cent had a clear-cut history of chest pain. When pain did occur, the most common site was in the midsternum, although it occurred in all parts of the chest and not infrequently in the upper abdomen. In the four cases having "discomfort only" the sensations were described as "constriction in the thorax," "dull ache in the chest," "precordial discomfort and feeling of constriction," "marked substernal pressure." None was associated with pain. The case histories of the four instances in which it was definitely known that the attack of coronary thrombosis was unassociated with any discomfort in the chest are of sufficient interest to merit brief description.

TABLE I

	RECENT INFARCTS		OLD INFARCTS	
Cases with pain	86	91.0 per cent	65	63.7 per cent
Cases with discomfort only	4	4.3 per cent	14	13.7 per cent
Cases without pain or discomfort	4	4.3 per cent	23	22.5 per cent

The first patient, a man aged sixty-four (Med. No. 22444), entered the ward greatly dyspneic and gasping for air and was asked if he had any pain. He cried, in answer, "No, I haven't any pain, but give me air!" He died a few minutes later and at autopsy had a large, very recent infarct near the apex of the heart in the left ventricle and no evidence of pulmonary embolism.

The second patient, a woman aged fifty (Med. No. 25374), had an incidental story of angina pectoris and was under observation for myxedema which was her primary complaint. She had been on the ward for several weeks and had been quite well during that time, when her condition suddenly changed. Without warning she became weak, semi-stuporous and was aroused with difficulty; her pulse became weak; heart sounds faint, and she "lay as if exhausted" for several days. After this she was very much improved and became well enough to sit up in a wheel chair. She denied having had any pain. Two weeks after the episode of weakness she died suddenly, and at autopsy there was found an infarct which contained necrotic muscle fibers and many phagocytic cells laden with pigment; in some areas the degenerated muscle fibers were being replaced with loose connective tissue. The appearance was of such an age that it could not have been the cause of sudden death, but from its appearance must have been several weeks old. There was no pulmonary embolus.

The third patient, a man aged seventy-four (Med. No. 2741), while in the excitement of hurrying to get a doctor for his wife, became suddenly short of breath, very weak, and it was necessary for him to sit down and rest several times before returning home. For several hours he continued to be weak and dyspneic and was nauseated but experienced no pain. Six days later he died suddenly. At autopsy there was a moderate sized, soft, necrotic infarct of the myocardium which had ruptured filling the pericardium with blood, causing his sudden death.

The fourth patient, a man aged seventy-seven (Med. No. 46956), with a history of a "feeling of depression in the chest with exertion and emotion" for two years, entered the ward complaining of weakness. He had signs of moderate cardiac decompensation, was given digitalis and twelve hours after admission was looking better, when he suddenly began to complain of increasing dyspnea. Respiratory difficulty, which was his only symptom, rapidly increased, and he died thirty minutes later without ever experiencing pain. At autopsy the right coronary

artery was completely occluded, and there was extensive recent infarction of the right ventricle. In addition there was an old infarct in the left ventricle near the apex. There was no pulmonary embolus.

It is of considerable interest that the most prominent symptom in two of these cases was the sensation of being short of breath, in another weakness was most prominent, and the other patient experienced both dyspnea and weakness.

GROUP OF "OLD" INFARCTS

The total number of old infarcts was 109. In seven of these cases the history was given by someone other than the patient. This occurred when the patient was brought to the ward in a comatose or irrational state and never regained consciousness, or when an emergency operation was to be performed from which the patient did not recover. In addition, there was one case in which the patient died outside the hospital, and the pathological specimen was brought in for examination without adequate history. Omitting these seven cases, which were not considered satisfactory in establishing whether the patient experienced pain with the infarct, there were 102 which had satisfactory histories (Table I).

There were 63.7 per cent of the patients who had a definite history of chest pain, 13.7 per cent with only a history of discomfort, and 22.5 per cent in whom there was no distress whatever. It is also of importance that 10 patients gave a history *only* of angina pectoris (that is, with transient pain of several minutes' duration) and had no story of the usual clinical appearance of coronary thrombosis. That this may occur was pointed out by Eppinger and Levine[6] in a recent communication.

The types of discomfort experienced by the group having a history of "discomfort only" were of considerable interest. They were described in the patients' own words, when possible, as follows: "sense of constriction in the chest," "some general discomfort in the abdomen," "biliousness which caused me to faint," "heart burn," "aching in the left chest, never severe," "dull pains in the abdomen," "gnawing at the lower end of sternum," "arm aches and numbness of the fingers of the left hand, of the left hand and arm," "tight band around lower part of chest pushing everything up," "substernal choking sensation and pressure in chest," "weight in chest," "tightness in chest," "indigestion and discomfort in stomach," "pressure in chest." It is surprising that infarction of the myocardium could give such a variety of sensations.

It is felt that the data obtained from the study of the old infarcts may not be as reliable as those of the recent infarcts. The first reason for this is that most of the patients were in the older age groups where memory defects may influence the recollection of a sensation experienced

in the past, especially if it was not severe. Secondly, it may well be that if a more deliberate inquiry had been made, a larger number would have been found to have experienced typical coronary pain or discomfort. However, this criticism partly loses its effectiveness when applied to the group of recent infarctions.

From this review it seems that there will be a small, but significant group of patients who had an old myocardial infarction from which they recovered, and in which there will be no history of chest pain or distress available to identify the attack. This percentage, it is felt, would be a good deal less than the 22.5 per cent found here with more careful analysis of the past history. Whether the incidence would be further influenced if minor infarctions less than 1 cm. in diameter were included, remains unanswered.

For the most part one can regard the old infarcts as synonymous with those from which recovery has occurred and the recent infarcts as the fatal ones. In this sense painless infarctions may be somewhat more frequent in the nonfatal than in the fatal group, but even here with more complete study the difference very likely will be only slight. These observations are mentioned because some authors have felt that painless infarction occurs almost entirely in those who have suffered from a previous attack.

SUMMARY AND CONCLUSIONS

A review was made of 200 consecutive autopsied cases of myocardial infarction. The purpose was to determine the incidence of painless cases of coronary thrombosis and the relative frequency of pain and other distressing symptoms in the chest. Most of the previously published reports, which have indicated that painless coronary thrombosis was of fairly frequent occurrence, have failed to take into account the difficulty of obtaining an adequate history under such conditions as sudden death, coma, surgical anesthesia, and cerebral vascular accidents. They have also omitted the important distinction between pain and other sensations equally characteristic of coronary artery disease, such as pressure, constriction, and burning.

The cases of myocardial infarction were divided into "recent" (and for the most part the immediate cause of death) and "old" (from which recovery for varying lengths of time occurred).

In the 200 cases of this series, when an opportunity was available to obtain an adequate history, it was found that only about 4 per cent of the attacks of myocardial infarction occurring within eight weeks before death were really painless. An analysis of the "old attacks" from which recovery had occurred showed that about 22 per cent were painless. It is believed that this figure would be a good deal lower if a more accurate account of the previous illness could have been obtained.

It was also found that about 4 per cent of the recent and about 14 per cent of the old infarctions were accompanied by sensations described by a variety of terms, such as, constriction in the chest, discomfort in the chest, burning, pressure, choking, or indigestion. About 10 per cent of the old infarctions had pain but not any more than is associated with an ordinary attack of angina pectoris. Ninety-one per cent of the recent and 64 per cent of the old cases had the classical pain of a coronary attack.

It was striking that about one third of the cases of acute infarction were accompanied by circumstances which made it impossible to elicit a history of pain. It is obvious that such cases cannot be classified in the painless group.

I wish to express my thanks to Professor Henry A. Christian and Dr. Samuel A. Levine for their aid in the preparation of this paper.

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THIOCYANATE THERAPY IN HYPERTENSION INCLUDING A NEW MICROMETHOD FOR DETERMINING BLOOD THIOCYANATES*

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ARTICLES by Barker[1, 2] appeared in March, 1936, and January, 1937, describing the use of thiocyanate in the treatment of hypertension. Although thiocyanate has been employed for this purpose for nearly ten years, occasional fatalities have been reported, with the result that its use had been abandoned almost entirely. Barker attempted to control the dosage by determining the level of thiocyanate in the blood. He tried to maintain a level, of 6 to 12 mg. per 100 c.c. of serum, but stated that mild toxic symptoms did not occur until the level rose above 15 mg., more marked symptoms above 20 mg., while fatalities probably occurred only with a level of 40 to 50 mg. He found that there was great variation in dosage required to attain the same blood level in different individuals and suggested that this might account for the fatalities reported in the literature. In his series of 45 cases controlled by blood determinations, he had no fatalities. Serious complications occurred in two patients in whom the blood level rose unexpectedly to 33 and 45 mg., respectively, on what appeared to be conservative dosage.

Approximately two weeks after the publication of Barker's first paper we began using his method in patients attending the Cardiac Clinic of the University Hospital. We have also treated a few patients from the wards of this hospital and from private practice. In the beginning we used Barker's method for thiocyanate determination. We found, however, that many patients objected to the repeated venipunctures required. Recently we have modified Barker's method so as to be able to use small amounts of blood such as can be obtained by finger puncture.

METHOD

General.—In the course of a year we have given thiocyanate to 26 patients. Sixteen of these have been followed for periods varying from two to nine months; they have attained satisfactory blood levels and have cooperated satisfactorily. The remaining 10 are not considered here because (1) a satisfactory blood level was not reached, usually because the patient discontinued visits, or (2) the time interval is

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inadequate to evaluate results. Cooperation has been much more satisfactory since introduction of the micromethod.

The initial dose employed is 0.1 gm. of potassium thiocyanate three times a day. We determine the thiocyanate level in the blood at the end of a week. The dose is then continued or, usually, increased. For example, in one case with the initial dose of 0.3 gm. a day, the level at the end of a week was 4 mg. per 100 c.c. The dose was then increased to 0.6 gm. a day, and at the end of a week the blood level was 8 mg. A final increase to 0.8 gm. a day was followed by a blood level of 10 mg. This we have regarded as optimal. If a blood level of 10 mg. is maintained for two weeks and no appreciable drop in blood pressure occurs, we abandon the medication.

We prefer to give the daily dose in three or four equal fractions rather than in a single dose. If the dose is high, it is well to take it in water to avoid gastric irritation. Aromatic elixir has been a satisfactory vehicle. We have used the potassium salt exclusively, although Barker stated the sodium salt is quite as satisfactory.

Arbitrarily we have defined a successful case as one in which the systolic pressure falls to 170 mm. or lower, with a corresponding decline in diastolic pressure and with associated subjective improvement.

Micromethod for Thiocyanate Determination.—

A. Solutions and materials

1. Ten per cent trichloracetic acid solution.

2. Ferric nitrate reagent. Dissolve 50 gm. of crystallized ferric nitrate in 500 c.c. of distilled water. Add 25 c.c. of concentrated nitric acid and make up to 1 liter with distilled water.

3. Thiocyanate standards. Stock solution. Dissolve about 1 gm. of potassium thiocyanate in 800 c.c. of distilled water. Titrate a 20 c.c. portion of a standard silver nitrate solution (made by dissolving exactly 2.92 gm. of silver nitrate in 1 liter of distilled water) acidified with 5 c.c. of concentrated nitric acid, with the potassium thiocyanate solution, using ferric ammonium sulphate as an indicator. Dilute the thiocyanate solution to a strength equivalent to that of the silver solution volume for volume; it then contains 100 mg. per 100 c.c. Standards may be made up from this by dilution as desired. We employ 10 mg. and 4 mg. per 100 c.c. to check against the ink standards, which will be described later.

4. Standards of ink. These standards are tedious to make up and are not absolutely necessary because standards of thiocyanate can be set up in small tubes for each working period. However, the ink standards do not fade, or at least have not done so yet, while the thiocyanate standards must be made up fresh each day. "Permanent" standards save at least one-half hour for each working period.

Yellow* and red† inks are used. In preparing the ink standards, thiocyanate standards are set up in test tubes, diluting from the stock solution described in Section 3 so as to have strengths per 100 c.c. of 4, 5, 6, 7, 8, 9, 10, 11, 13, and 15 mg. Each solution is then mixed with an equal volume of trichloracetic acid and one-fifth of the combined volume of ferric nitrate reagent.

The two inks, a few drops at a time, are added slowly to approximately a liter of water in a clear container. The approximate proportion was two parts of the red

*Indelible yellow ink made by F. Weber and Co., Philadelphia.
†Higgins Brick Red Waterproof Ink.

to one part of the yellow. From time to time a little is taken out in a test tube and compared with the 15 mg. thiocyanate standard. When the colors appear comparable except that the ink is a little deeper (about 10 to 20 per cent), the solutions are compared in a colorimeter, and a reading of the ink in terms of thiocyanate is obtained. A small amount, approximately 50 to 75 c.c., is then diluted to match exactly the thiocyanate standard of 15 mg. A small amount of this, after it is checked in the colorimeter, is sealed in a glass tube such as that to be used in the actual determination. We use tubing with a 4 mm. outside diameter, a 1.5 mm. inside diameter, and a capillarity in ether of 5 mm. Tubes of the ink standard are compared with tubes from the thiocyanate solution. When the match is satisfactory, the remaining tube standards are made up similarly.

5. A number of glass tubes, drawn to a capillary tip at one end, cut off evenly at the other, about 10 cm. long, with measurements for width as given for the standard tubes. The tubes used to collect blood are coated with potassium oxalate (i.e., a solution of 2 per cent potassium oxalate is sucked up, blown out, and the tubes are permitted to dry). The tubes used for the reactions with the plasma are clean.

B. Actual Determination:

1. Collect blood in tube containing potassium oxalate. A column of blood from 6 to 7 cm. long is drawn up through the capillary tip, which is then sealed.

2. Centrifuge. Divide the tube with a file at the cell-plasma junction. Transfer the plasma to a clean tube.

3. Measure the length of the plasma column. Add a similar length of trichloracetic acid. Seal the capillary end. Mix with a wire. Let stand for ten minutes.

4. Centrifuge.

5. Divide the tube at the precipitate-supernatant fluid junction. Transfer the clear supernatant fluid to a clean tube.

6. Add a column of ferric nitrate reagent one-fifth the length of the column of supernatant fluid. Seal the capillary tip. Mix with a wire.

7. Compare, against the colorimeter light, with the standard tubes, using either freshly made up thiocyanate standards as described in paragraph 4 under "Solutions and materials" or the permanent ink standards. When the inks are used, we check them by making up at semiweekly intervals thiocyanate standards of 4 and 10 mg. for comparison. We have found the ink in sets of tubes constant for at least two months.

Certain points in the handling of such tubes are important. In the first step the blood is introduced through the capillary end and sucked up, by a rubber tube and mouthpiece attached to the wide end as for a blood counting pipette. Before sealing the capillary tip the rubber tube is pinched twice, the first time near the glass tube and the second just distal to the first pinch, releasing the first pinch only after the second has been applied. This draws the blood away from the capillary tip, which is then sealed. When breaking the tube to separate the plasma after centrifuging (step 2), the finger must be applied tightly over the open end or the plasma will run out. Transfer of liquid from one tube to another is made by thrusting the capillary tip of the recipient tube into the lumen of the donor tube and tilting both tubes slightly from the horizontal so that the liquid runs into the recipient tube. Before adding a second reagent, as in steps 3 and 6, move the column from the capillary tip to within 1 cm. of the wide end; this is best accomplished by putting a rubber tube on the capillary end and pinching it progressively nearer the tube. When the rubber tube is released, the fluid should flow readily with slight tilting. If it does not, there is usually a bubble in the capillary tip which must be expelled, either by moving the column backward and forward while applying absorbent cotton to the capillary end or by gentle heat. The mark to which the second reagent is

to be added is made with a file and pencil. The finger is placed over the capillary end, the tube is held vertical with the capillary end up, and the open end is thrust deeply into a test tube containing the reagent to be added. Slight movements of the occluding finger then permit the reagent to rise to the mark designated. An air bubble separates the two columns. Both columns are then permitted to move slightly away from the wide end, by tilting, so that there will be no spill over when the capillary end is heated. The capillary tip is then sealed, and the two columns are mixed with a wire. In step 5 it is important to make sure that the precipitate is evenly packed, i.e., that there are no isolated lakes of plasma below the upper level of the precipitate. If such are present, the tube must be stirred and recentrifuged. Otherwise the reading will be too low.

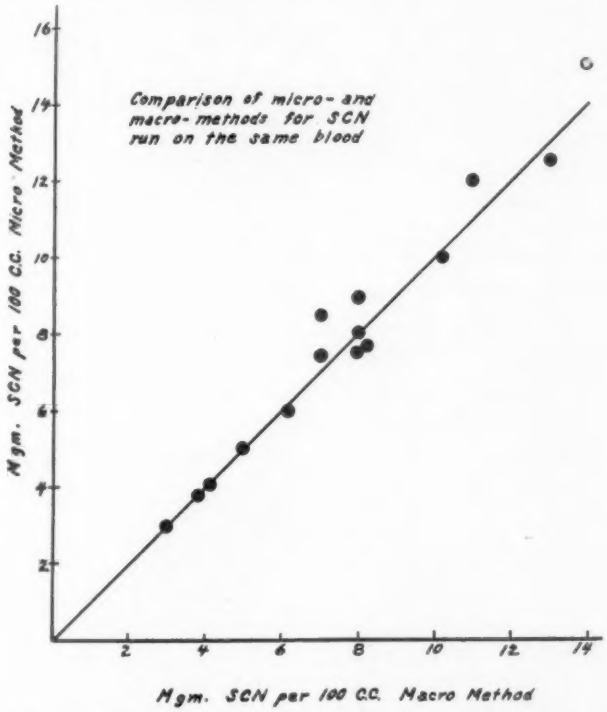

Fig. 1.—Chart showing comparison between blood thiocyanate values obtained in the same patient at the same time by Barker's method and by the micromodification.

RESULTS

For comparison of readings made at the same time in the same patient by the method of Barker and by our micromodification see Fig. 1. Obviously the micromethod is less exact and can be read only to the nearest milligram. However, for clinical purposes, it is adequate. The level we wish to reach, approximately 10 mg., is 5 mg. below the level at which, according to Barker, mild toxic symptoms occur, 10 mg. below the level of definite toxic symptoms, and 30 mg. or more below a level which is thought to be fatal. Thus the margin of safety is large.

The data concerning the 16 patients adequately treated are listed in Table I. The first ten would be considered good cases according to the

TABLE I

CASE	SEX	AGE	DURATION (YEARS) HYPERTENSION	BEFORE TREATMENT BLOOD PRESSURE SYSTOLIC		AFTER TREATMENT BLOOD PRESSURE SYSTOLIC		AV. LOWERING	*DURATION (WEEKS) OBSERVATION	†SUBJECTIVELY	DISC CHANGES	RENAL DAMAGE	BLOOD CYANATE LEVEL MG./100 C.C.	DAILY DOSAGE GM.
				RANGE	AV.	RANGE	AV.							
1	F.	37	3	178-210	190	118-176	150	40	24	I	0	0	7-13	0.6
2	F.	43	2	174-230	190	150-180	164	26	5	I	0	0	11	0.8
3	F.	51	3	175-212	190	138-164	150	40	20	I	0	0	10	0.6
4	F.	49	7	215-230	220	162-168	165	55	14	I	0	0	8	0.6
5	F.	33	12	210-238	230	168-182	170	60	10	I	0	0	9	0.8
6	F.	52	4	225-235	230	150-165	160	70	23	I	0	0	9.5	0.8
7	F.	43	10	190-220	195	150-165	160	35	39	I	0	0	10	0.8
8	M.	53	1	200-240	220	130-190	165	55	9	I	0	0	13	0.6
9	F.	46	1	180-225	215	168-174	170	45	4	I	0	0	10	0.8
10	M.	34	2	200-220	210	165-178	170	40	7	I	0	0	10	1.0
11	F.	46	7	200-250	220	174-206	190	30	13	I	0	0	4-8	0.4
12	F.	70	9	190-250	240	194-210	200	40	16	U	0	0	10-13	0.3
13	F.	63	3	182-240	220	178-184	180	40	12	I?	0	0	8.5	0.4
14	F.	35	8	200-240	220	178-206	182	38	18	W		Sl.	11	0.4
15	F.	40	6	220-275	250	228-252	240	10		U	0	Sl.	11	0.8
16	F.	31	5	220-275	230	210-240	230	0		U	Sl.	0	10	1.0

*Duration (weeks) observation refers to the period beginning with the lowering of the blood pressure to 170 or less with a satisfactory blood cyanate level, and ending with the time of writing this article.

†Subjectively: I—improved; U—unchanged; W—worse.

definition previously given. In Cases 11 to 13 the blood pressures were somewhat lowered but not to the desired level, while the patients either felt better or at least were no worse. These cases might be classed as equivocal. Cases 15 and 16 are classed as failures because there was no effect on blood pressure. Case 14 is also considered a failure because, although the blood pressure was lowered somewhat, the patient felt worse.

Patient 7 is charted in detail in Fig. 2. This woman, aged forty-three years, was known to have had a hypertension averaging about 195 mm. systolic since 1927. It had been taken many times by her husband, a physician, but for simplicity the figures charted include only those ob-

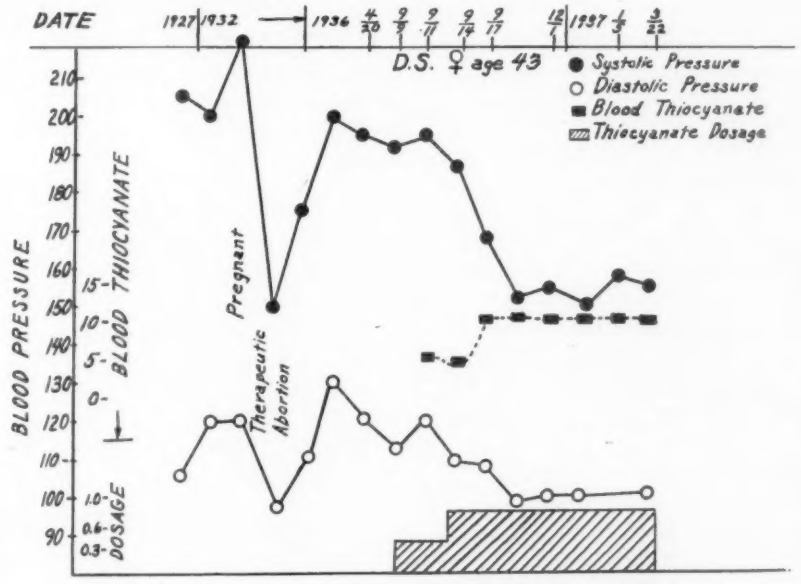

Fig. 2.—Chart of Patient 7. For details see text.

tained on visits to our clinic. Many forms of treatment, including sedatives and endocrine products, had been tried without effect. The only period when the systolic blood pressure reached 150 immediately followed a therapeutic abortion. She had been more or less invalided for years, with recurring headaches and bouts of nausea. On thiocyanate therapy her blood pressure has ranged between 150 and 165 for nine months, and her headaches and attacks of nausea have disappeared. She is leading a normal life.

While analysis of such a small series is of doubtful significance, our results conform with those obtained by Barker. We have had no fatal results and no major complications of any sort. Two patients (Cases 6 and 11) developed a little pruritus with the larger doses. One patient (Case 12) had a mild gastrointestinal upset which may or may not have

been due to the drug. Patient 14 felt worse when her blood pressure was lowered, but no complications were noted.

SUMMARY

Thiocyanate was given to 26 patients with hypertension. The dosage was controlled by blood thiocyanate determinations according to the principle of Barker. No fatalities and no major complications occurred. Of the 16 patients adequately treated and controlled, 10 had a good result: i.e., systolic blood pressure fell to 170 or lower, with a corresponding fall in diastolic pressure, and there was subjective improvement. Dosage varied from 0.3 to 1.0 gm. a day. The blood thiocyanate level varied from 8 to 13 mg., though 10 mg. was the level desired. A micromodification of Barker's blood thiocyanate method was devised using standards of ink which seem to be relatively permanent. This method utilizes blood from finger puncture rather than venipuncture and is sufficiently accurate for clinical requirements.

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RECIPROCAL RHYTHM IN A PATIENT WITH CONGENITAL HEART DISEASE*

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PROVIDENCE, R. I.

DURING the study of electrocardiograms showing unusual transitions between normal sinus rhythm, ventricular escape, A-V nodal rhythm, and A-V dissociation,[1] one patient was encountered whose electrocardiograms on several occasions exhibited reciprocal rhythm. As it was possible to observe this patient over a considerable period, and as reciprocal rhythm is a rare condition, at times incorrectly diagnosed,[2] a brief report of this case seemed advisable.

CASE REPORT

M. S., a twenty-three-year-old hospital employee, was admitted to the Rhode Island Hospital Oct. 15, 1934, complaining of vomiting, diarrhea, and general malaise of one day's duration. He gave a history of previous gastrointestinal upsets following the ingestion of pork or ham, and he had eaten pork for lunch on the day prior to entry. On the day of entry he felt uncomfortable generally and developed progressive nausea and, somewhat later, diarrhea. There were no complaints referable to the cardiovascular system.

Past History.—He had always been well. There was no history of rheumatic fever, chorea, or epistaxis. He had never noted or been told of periods of cyanosis. He had noted no dyspnea, and, during the summer prior to admission, had frequently swum over a mile without difficulty. After vigorous exertion he was occasionally conscious of mild palpitation.

Physical Examination.—The patient was a very well-developed and well-nourished young white male, lying comfortably in bed. Temperature was 104.6° F.; pulse, 80; and respiration, 25. The significant positive findings were limited to the chest. The heart was definitely enlarged to the left by palpation and percussion. No thrills were felt, but a distinct shock could be felt in the region of the pulmonic valve and along the left sternal border. Upon auscultation this shock was found to be synchronous with a very loud pulmonic second sound. With full inspiration this pulmonic second sound became reduplicated. The only murmur present was a 2 to 3 plus (4 plus = maximum) systolic murmur, loudest along the left sternal border in the third and fourth interspaces. The rhythm was variable, at times being regular and at times exhibiting coupled beats. The coupled beats were more apt to appear during the maintenance of full inspiration. The heart rate varied between 50 and 90 beats a minute, and the blood pressure was 115/60.

Laboratory Studies.—Urine studies were negative. The Wassermann test was negative. Microscopic blood studies were normal except for a leukocytosis of 21,000 with 80 per cent polymorphonuclear cells. The stools showed occult blood on one occasion. Subsequent examinations were negative. No ova or parasites were seen.

Course and Further Studies.—The temperature rapidly dropped to normal and the gastrointestinal disturbance disappeared in two to three days. After the tempera-

*From the Heart Station of the Rhode Island Hospital, under the direction of Dr. Frank T. Fulton.

ture dropped, bigeminy occurred less frequently. Orthofluoroscopic studies of the chest showed the heart diameter to be 14.9 cm. and the internal chest diameter to be 25.4 cm. There was definite enlargement of the left ventricle both to the left and posteriorly. No enlargement of the left auricle was detected. There was increased prominence in the region of the pulmonary conus. The cardiac pulsations were slow and vigorous.

The patient was soon discharged from the ward with a diagnosis of acute enteritis and congenital heart disease, probably patent interventricular septum. He has continued in the employ of the hospital, is in excellent health, and has developed no new symptoms or signs (March 15, 1937). Occasional electrocardiograms taken during the past two years have shown, for the most part, S-A rhythm. At times A-V nodal rhythm has occurred, but reciprocal rhythm has not appeared spontaneously in the tracings taken.

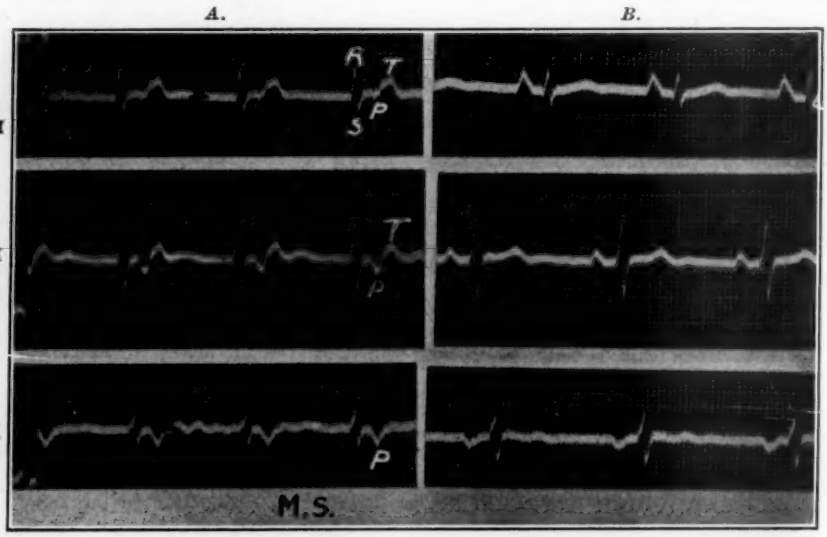

Fig. 1.—Tracing *A*, at the left, was recorded while the patient was exhibiting uncomplicated A-V nodal rhythm. It was taken Oct. 31, 1934, forty-five minutes after the subcutaneous administration of atropine, grain one-thirtieth. The rate was 70 per minute. Tracing *B*, at the right, was recorded while the patient was exhibiting uncomplicated S-A rhythm. It was taken Oct. 20, 1934, during bed rest without previous medication. The rate was 55 per minute. In Lead I note the nearly isoelectric P-waves in tracing *A* and the high P-waves in tracing *B*.

ELECTROCARDIOGRAPHIC STUDIES

Fifty-eight electrocardiograms were taken on this patient under various circumstances, and, of this number, thirteen showed one or more instances of reciprocal rhythm. The remainder were about equally divided in showing S-A and A-V rhythm.

In reviewing the tracings it was noted that the transitions between S-A and A-V rhythm were frequent and would often occur spontaneously. Consequently, it was difficult and often impossible to attribute the presence of any one type of rhythm to any procedure employed or drug administered. The effect or lack of effect of various conditions and drugs is outlined below.

Fever: Reciprocal rhythm was frequently present during the short time that the patient's temperature was significantly elevated. Whether this was due to the fever, or to infection or toxemia, we do not know. No subsequent febrile episodes have been present to date.

Ingestion of Cold Water: No definite effect was noted.

Change of Posture: This involved taking records with the patient sitting up and immediately after lying down. The reverse procedure was also tried. No consistent change was noted.

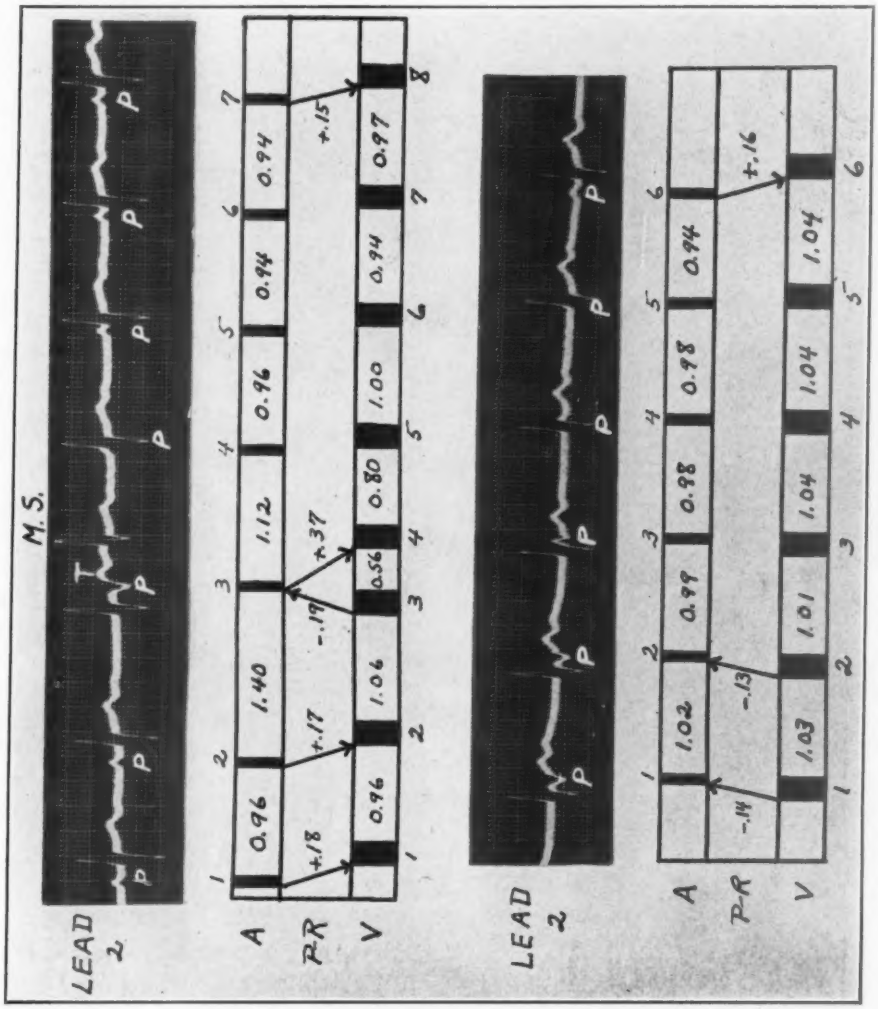

Fig. 2.

Fig. 2.—These two tracings in Lead II show the transitions in rhythm that frequently appeared spontaneously in this patient. The top tracing, taken Oct. 19, 1934, shows the sudden appearance of a reciprocal beat in the midst of S-A rhythm. The bottom tracing, taken Oct. 20, 1934, shows a transition from A-V to S-A rhythm.

The diagrams beneath this and subsequent electrocardiograms are arranged in identical fashion and may be described together. The vertical black bars in the upper strip, marked *A*, represent the auricular beats and are placed directly beneath the P-waves in the accompanying electrocardiogram. In the middle strip, marked *P-R*, are recorded, in hundredths of a second, the P-R intervals (preceded by a plus sign) or the R-P intervals (preceded by a minus sign). The arrows in this middle strip indicate the direction of impulse conduction and are only included when it seems probable that a beat has been actually conducted. In the bottom strip, marked *V*, the heavy vertical bars represent and are placed directly beneath the ventricular beats. The intervals between the auricular and ventricular beats are recorded in hundredths of a second. The auricular and ventricular beats are numbered consecutively in each diagram.

Carotid Sinus Pressure: This was tried on each side on several occasions, and no constant effect was elicited.

Exercise to the point of mild dyspnea resulted in rhythm of either S-A or A-V origin, at a somewhat increased rate. The ventricular rate (85 per minute) was quite equal to that present when the temperature was elevated and when reciprocal beats were frequent.

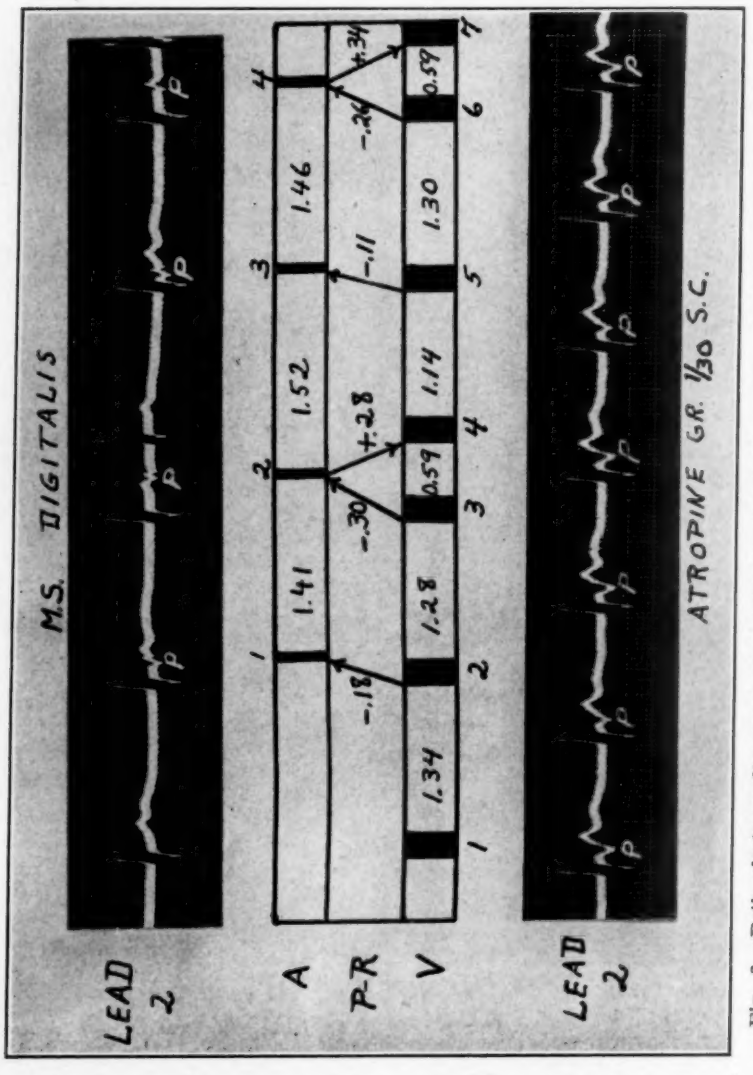

Fig. 3.—Both electrocardiograms were taken in Lead II on Dec. 10, 1934. The top tracing was taken after the administration of large amounts of digitalis over a period of thirty-three days. Several other control tracings on this day showed reciprocal rhythm. The bottom tracing was taken thirty minutes after the subcutaneous administration of atropine, one-thirtieth grain. The reciprocal rhythm was abolished and A-V nodal rhythm appeared. Later, as the effects of the atropine wore off, reciprocal rhythm reappeared.

Adrenalin: Twelve minims (1-1000 solution) were injected subcutaneously on one occasion. This raised the rate per minute from 53 to 65 in fifteen minutes. All of several tracings made after the injection showed S-A rhythm. However, the control tracing on this day also showed S-A rhythm, so no convincing evidence is present that this amount of adrenalin had any appreciable effect.

Forced Deep Respiration: On several occasions this was tried and almost always resulted in A-V rhythm. Occasionally, especially after a forced expiration, reciprocal rhythm occurred. Except for the administration of digitalis (Fig. 3), temporary

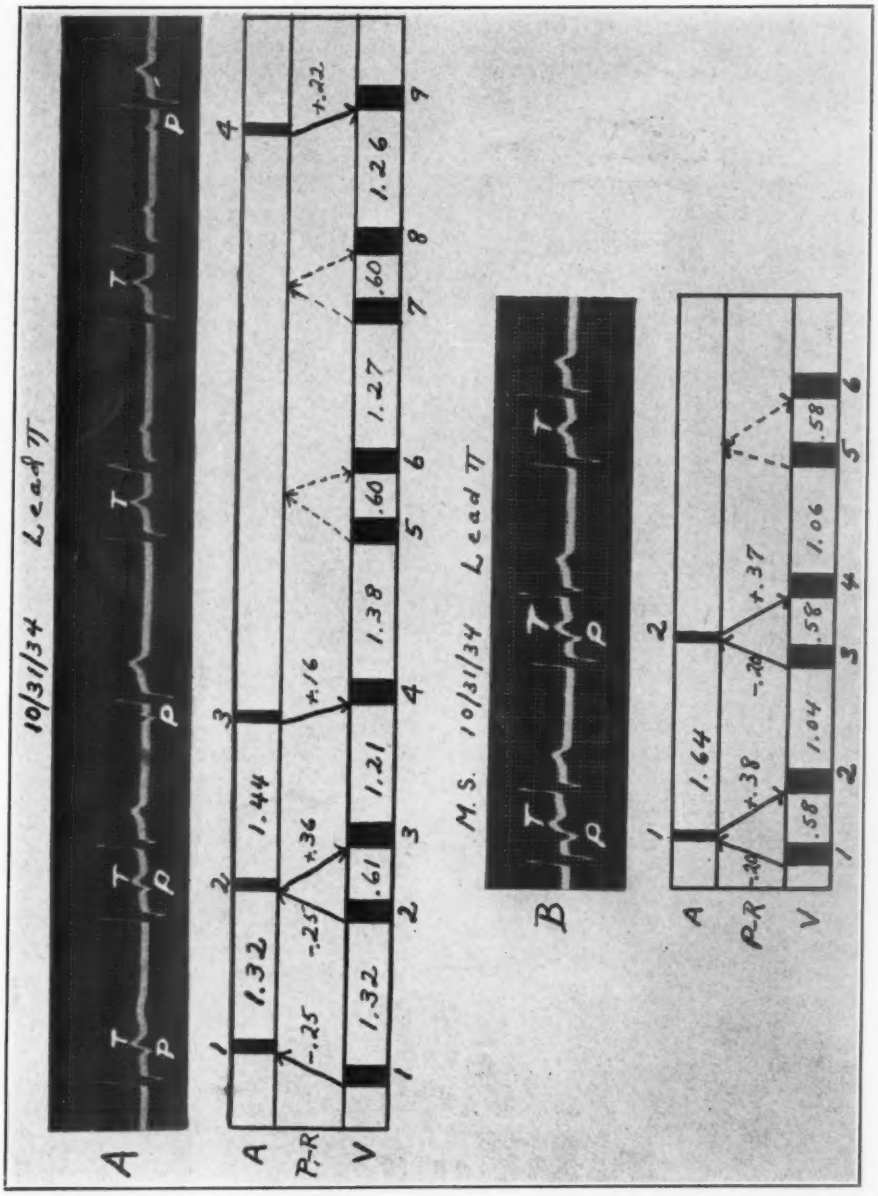

Fig. 4.

Fig. 4.—Both electrocardiograms were taken Oct. 31, 1934, in Lead II. The longer tracing *A* was a control electrocardiogram taken before the administration of atropine. Note the reciprocal beat (ventricular beats 2 and 3) and later the two couples (ventricular beats 5 and 6, and 7 and 8). In the two latter instances observe the absence of clear evidence of auricular activity between the two beats of the couple, and the slurring of the second ventricular beat in each pair. See discussion in text.

The shorter tracing *B* was taken twenty minutes after the administration of one-thirtieth grain of atropine subcutaneously, while right carotid sinus pressure was being applied. Here recurring reciprocal beating is present. Note the absence of the P-wave between ventricular beats 5 and 6. In all three couples the interval between the two ventricular beats is constant.

TABLE I

The time relations of the various components of the reciprocal beats observed in Leads II and III. Those observed in Lead I were not included, as the P-waves were often difficult to clearly identify. Note the constancy of the R-R interval, and the variability of the P-R and R-P intervals, observed on Dec. 10, 1934. Also note the variability in the character of the second QRS complex.

DATE AND LEAD	R-R INTERVAL (SECONDS)	R-P INTERVAL (SECONDS)	P-R INTERVAL (SECONDS)	CONDITION OF SECOND QRS
10/16/34				
Lead II	0.57	0.22	0.35	R lower, S deeper
Lead II	0.56	0.22	0.34	R lower, S deeper
Lead III	0.60	0.20	0.40	No change
Lead III	0.58	0.21	0.37	No change
10/19/34				
Lead II	0.56	0.19	0.37	R higher, S smaller
10/31/34				
Lead II	0.64	0.25	0.39	Slurred, R higher
Lead II	0.62	0.22	0.40	No change
Lead II	0.60	0.24	0.36	No change
Lead II	0.60	0.22	0.38	No change
Lead II	0.59	0.20	0.39	Much slurred
Lead II	0.59	0.28	0.31	Much slurred
Lead II	0.60	0.22	0.38	No change
Lead II	0.62	0.21	0.41	R higher, no S
Lead II	0.62	0.20	0.42	R higher, slurred
Lead II	0.61	0.28	0.33	No change
Lead II	0.56	0.19	0.37	No change
Lead II	0.61	0.25	0.36	R higher, S smaller
Lead II	0.58	0.20	0.38	R higher, S smaller
Lead II	0.58	0.20	0.38	R higher, S smaller
11/ 1/34				
Lead II	0.64	0.28	0.36	Slightly slurred
Lead II	0.64	0.28	0.36	Slightly slurred
Lead II	0.63	0.27	0.36	Slightly slurred
Lead II	0.61	0.38	0.23	S deeper
Lead III	0.60	0.21	0.39	Much widened
12/ 4/34				
Lead II	0.60	0.23	0.37	Slightly slurred
12/ 8/34				
Lead II	0.62	0.26	0.36	No change
Lead II	0.66	0.26	0.40	No change
Lead III	0.60	0.26	0.34	R higher
Lead III	0.61	0.26	0.35	R higher
Lead III	0.60	0.22	0.38	R higher
Lead III	0.62	0.24	0.38	No change
Lead III	0.60	0.28	0.32	No change
12/10/34				
Lead II	0.59	0.30	0.29	R higher, S smaller
Lead II	0.60	0.23	0.37	R higher, S smaller
Lead II	0.59	0.25	0.34	R higher, S smaller
Lead II	0.60	0.30	0.30	R higher, S smaller
Lead II	0.60	0.24	0.36	R higher, S smaller
Lead II	0.60	0.24	0.36	R higher, S smaller
Lead II	0.60	0.25	0.35	R higher, S smaller
Lead II	0.59	0.27	0.32	R higher, S smaller
Lead II	0.60	0.19	0.41	R higher, S smaller
Lead II	0.59	0.26	0.33	R higher, S smaller
Lead III	0.60	0.33	0.27	R much higher
Lead III	0.60	0.32	0.28	R higher
Lead III	0.60	0.28	0.32	R higher
Lead III	0.60	0.20	0.40	R much slurred
Lead III	0.60	0.28	0.32	R higher
Lead III	0.60	0.34	0.26	R higher
Maximum difference in figures	0.10	0.19	0.19	

maintenance of full expiration seemed to be the procedure most likely to result in reciprocal rhythm. Wilson[3] has noted instances of a shift of the pacemaker from the S-A to the A-V node with deep respiration.

Digitalis: Four-and-one-half grains a day were given by mouth for twenty-one days. At the end of this time there were no discernible effects by electrocardiogram, and no symptoms. Consequently, the daily dose was raised to six grains, and this was continued for another twelve days. There were still no toxic symptoms, and the patient's appetite remained excellent. However, at this time, the electrocardiogram showed frequently recurring examples of reciprocal rhythm (Fig. 3). Previous electrocardiograms taken during the period of digitalis administration had shown, for the most part, A-V nodal rhythm. White,[4] Dock,[5] and Blumgart and Gargill[6] have observed the more frequent occurrence of reciprocal rhythm after digitalization.

Atropine: This was administered subcutaneously in one-thirtieth grain doses on two occasions, once before giving digitalis and once at the end of the experiment with digitalis. In the first instance, the control tracing showed transitions between S-A and A-V nodal rhythm. Tracings were taken 20 minutes, 45 minutes, 85 minutes, 4½ hours and 24 hours after the injection of atropine. The first three of these showed A-V nodal rhythm throughout, with a moderate increase in the ventricular rate. The last two tracings, taken when the symptomatic effects of atropine had worn off, were very similar to the control tracing. No consistent tendency to reciprocal rhythm was shown at any time. Jones and White[7] noted a similar lack of effect of atropine in changing A-V rhythm. Wilson[8] has pointed out the tendency of atropine, especially soon after its administration, to convert S-A into A-V rhythm. Bishop,[9] and Dock,[5] however, observed a change from A-V to reciprocal rhythm, following the administration of atropine.

The effect of atropine after digitalis administration was more striking. Tracings were taken 15, 17, and 30 minutes after injection. In all three tracings only A-V nodal rhythm appeared, and the previously observed tendency toward reciprocal rhythm had entirely disappeared (Fig. 3). White,[4] and Blumgart and Gargill[6] have observed the shortening by atropine of R-P intervals previously lengthened by digitalis.

A study of the time relations of the various components of reciprocal rhythm is recorded in Table I. It is readily seen that the interval between the two ventricular beats of a couple is fairly constant throughout. The R-P and P-R intervals, however, show greater variation. Moreover, the length of the R-P interval does not appear to be the sole determining factor in the appearance of reciprocal rhythm. In general, reciprocal rhythm does occur with the longer R-P intervals. However, in some tracings, R-P intervals not followed by reciprocal beats are as long as, or longer than, R-P intervals followed by typical reciprocal beats. The second QRS of a couple often differs somewhat from the first. It may show slurring of greater or less degree, and the relative amplitude of the R- or S-waves may be distinctly different from that seen in the first QRS complex.

DISCUSSION

It is not our purpose to enter into a detailed discussion of the mechanism of reciprocal rhythm, as this has been done previously by others[4-6, 10-13] and we have nothing to add. One point in Figure 4*B* seems worthy of further comment, as it illustrates an observation that we have not encountered in the literature on this subject. It may be noted that the first two groups of coupled beats in this tracing have a definite inverted auricular wave between the two beats of the couple—as is usual in reciprocal rhythm. However, between the beats of the last couple

(ventricular beats 5 and 6) there is no definite evidence of any auricular activity. In spite of this, the interval between the ventricular beats remains the same as in the previous couples (0.58 second). This we take to be suggestive evidence that an impulse may travel up the A-V node or bundle *without* entering the auricle, and return by the same or a slightly different pathway to result in a ventricular response, after an interval equal to that taken by similar impulses that do activate the auricles. This would thus seem to be evidence that auricular systole is not necessary for the occurrence of the second ventricular beat in reciprocal rhythm.

Coupled beats similar to the last one illustrated in Fig. 4*B* were observed on two other occasions and are shown in Fig. 4*A* (ventricular beats 5 and 6, 7 and 8). There are two differences to be observed, however. QRS complexes 6 and 8 are considerably slurred, and the T-waves within the couples are more pointed than those seen elsewhere in the tracing. The widened QRS complexes indicate that the impulse has spread through the ventricles differently than in the ordinary beats. However, this point would not by itself militate against a diagnosis of reciprocal rhythm, as we have several otherwise typical instances of reciprocal beating in which the second beat of the couple shows marked slurring. Dock,[5] and Blumgart and Gargill[6] have also observed slurring of the second QRS complex in reciprocal rhythm. The unusual shape of the T-waves indicates the possibility of upright P-waves of S-A origin being buried within them. However, here again, the intervals between the beats of the two couples are practically identical with the interval between the beats of a typical example of reciprocal rhythm shown in the first part of the tracing (ventricular beats 2 and 3). This would suggest that the mechanism of all three couples is much the same. Thus, we believe, the evidence is suggestive that an impulse may travel from the ventricles back to the auricles and return to the ventricles without resulting in an auricular beat. However, further study is necessary to conclusively prove or disprove this point.

SUMMARY AND CONCLUSIONS

A case of congenital heart disease with probable patent interventricular septum is presented. Electrocardiograms frequently showed reciprocal rhythm.

During the patient's initial febrile episode, reciprocal rhythm appeared spontaneously on several occasions. Of various experimental procedures tried, only forced respiration and the administration of large amounts of digitalis seemed effective in initiating this type of rhythm. Atropine abolished the effect produced by digitalis and resulted in A-V nodal rhythm.

In the reciprocal rhythm shown by our patient, the second ventricular beat followed the first after a fairly constant interval. The R-P and P-R intervals of the intervening auricular beats were more variable.

Evidence is presented suggesting that reciprocal beats may occur without the presence of a preceding auricular beat.

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STUDIES OF THE COLLATERAL CIRCULATION FOLLOWING EXPERIMENTAL VASCULAR OCCLUSION*

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THIS investigation was undertaken with the purpose of producing vascular obstruction in the rabbit—to follow from inception to termination the changes that occur—and to evaluate the factors which influence the development and effectiveness of the collateral circulation. A major portion of the study was devoted to the effect of passive vascular exercise.

PROCEDURE

The ears of mature rabbits were selected because they, like the extremities, are peripheral organs; and because temperature and color changes of the skin could be readily correlated with changes in the caliber of the vascular tree.

Groups of animals were prepared and then treated according to the following schema: (Table I.)

TABLE I

GROUP	NO. OF RABBITS	PASSIVE VASCULAR EXERCISE	REMARKS
I	1 normal control 1 ligated control	Pressures: -30 -20 -80 -30 Cycle: 30″ negative 10″ positive Rx: 15 to 60 min.	Surface and vascular reactions.
II	1 ligated control 3 ligated test animals	Pressures: -30 -40; -20 3 wk. treatment ½ hr. to 1 hr. daily	Ligation of main vessels at base of ear only.
III	1 ligated control 3 ligated test animals	Pressures: -30 -10 1 hr. daily for 1 mo.	Ligation of main vessels at base of ear and also at level of middle of ear.
IV	1 ligated control 2 ligated test animals	Pressures: -30 -10 1 hr. daily 2 mo. treatment	Very complete ligation of main branches at several levels. Development of gangrene on treated side 1 to 2 weeks after start of treatment.

The individual animals presented the normal (ear) circulatory pattern for rabbits, i.e., a central artery and two marginal branches, one mesial and one lateral. These ramify profusely and anastomose very freely so that an intimate vascular network is formed. The veins closely parallel the arterial side of this system.

Preparation of Animals.—A through-and-through mass ligature was made at the base of the ear around each of the main vessels until they ceased to pulsate. The animals were anesthetized with ether prior to the operation. A week was permitted

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to elapse to permit thrombosis and organization of the thrombus, as well as subsidence in the local reaction to the ligatures.

Methods of Study.—1. Surface reactions, i.e., changes in skin temperature, color and tissue necrosis, were observed daily.

2. Vascular changes were recorded by means of photographic and arteriographic studies. For the former, the animal was placed in a box with a sliding cover so that only its head projected above the surface. Back of the ears and supporting them was a thick rectangular glass jar filled with water. The ears were kept together by a small piece of adhesive plaster. With illumination coming through the glass jar from behind, the vascular tree was shown up very effectively, and the heating effects eliminated. The usual photographic factors of exposure time, aperture, distance of object from lens, and illumination were kept constant. For the arteriographic studies, the animal was anesthesized with ether. A rubber tourniquet was placed tightly around the abdomen just below the costal cage to cut off the blood supply to the lower half of the body. An intracardiac injection of 3 c.c. of thorotrast was made under sterile precautions, and x-ray films of the ears were taken. The anesthesia and the intracardiac injection could be repeated within a few days without danger. Many of the animals received as many as 5 or 6 such treatments.

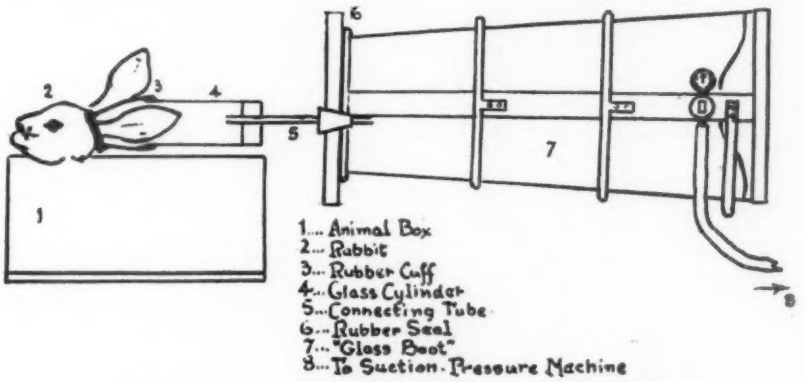

Fig. 1.—Apparatus and position of animal during treatment.

At the termination of each experiment the animals were killed with ether, and a dissection of the neck organ was made to isolate the carotid arteries. These were injected with a solution of thorad (1:1 dilution) to which had been added a few drops of methylene blue, the latter to show when filling of the arterial tree had been completed.

Treatment by passive vascular exercise had to be adapted to the experimental animal. Fig. 1 illustrates the setup. A rubber cuff was placed loosely over the ear of the animal so that the soft rubber sponge base rested snugly against the side of the skull. Compression of the vessels mechanically by the cuff was therefore eliminated. A rubber cork was inserted into the external ear so that pressure changes would not be communicated directly to the internal ear. The cuff was attached to a glass cylinder which in turn was connected to the "boot" by means of a piece of glass tubing.

OBSERVATIONS

The ears of a rabbit are a very sensitive indicator of the bodily reactions due to internal and external stimuli. They may droop or be erected instantly, and a process of alternate blanching and flushing goes on constantly for variable intervals. When a normal ear is sub-

jected to passive vascular treatment (–30 –10 mm. Hg) for a half hour or longer it becomes definitely cyanotic and is cold to the touch. The untreated ear does not become cyanotic and remains warmer than its treated mate. Increasing the pressure to –80 –20 mm. Hg produces a proportional increase in the intensity of the cyanosis and the coldness of the ear. The higher the initial pressure the more rapidly are these changes produced. When treatment is stopped, the color and skin temperature of the ear return very quickly to normal within a few minutes. When ears of ligated animals are subjected to the same treatment, the surface changes in general are similar to those above.* However, there is a quantitative difference—the cyanosis is more intense—a definite blue or even a slate gray. In addition, the return of the

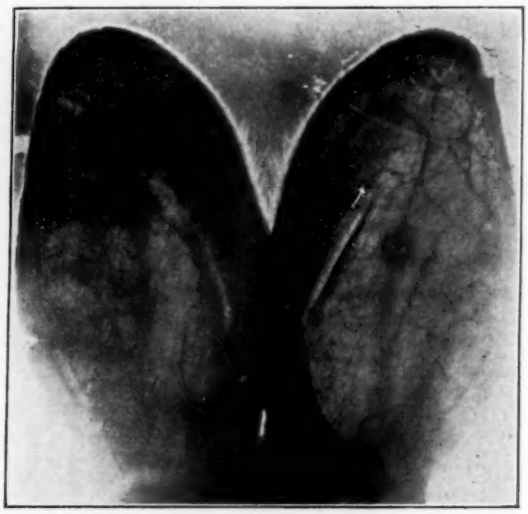

Fig. 2.—Intense cyanosis of treated ear. Also notice blurring of the larger vessels and sparseness of smaller branches.

treated ear to its resting state may take from fifteen minutes to several hours. Cyanosis is last to disappear; the return of the skin temperature is more rapid (Fig. 2).

Immediately after the ligation of the main vascular trunks, the ear becomes cold, white, and lifeless. Within a few days it begins to return to the normal state. Although there are no longer any pulsating vessels, the ear feels warm and flushes as readily as it does normally. The large vessels are definitely narrowed but there is present a marked increase in the number of small collateral branches. This is best exemplified by the following arteriograms: Figs. 3 and 4 on a normal control, Figs. 5 and 6 on a ligated control. In the former, the vascular network follows a definite pattern; branching and sub-branching occur regularly and the vessels themselves are of uniform caliber and smooth

*In the illustrations, the treated ear will always be found to the left.

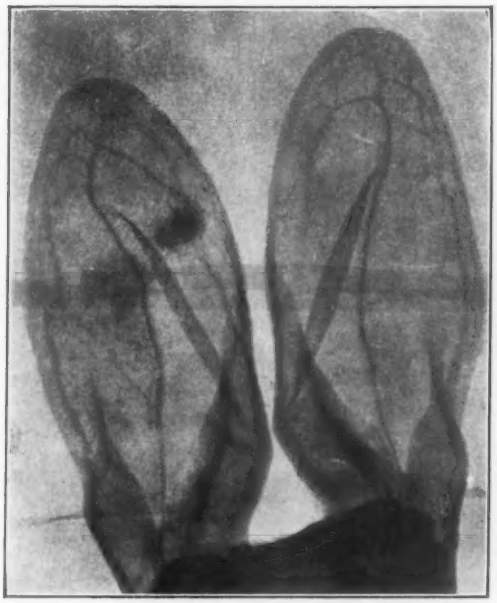

Fig. 3.—Arteriogram (in vitro) of a normal control. Vessels are smooth in outline and subdivisions occur regularly.

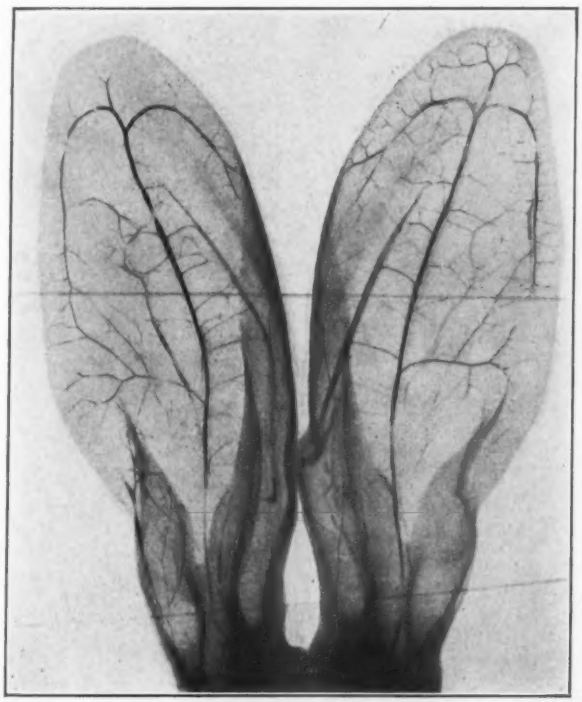

Fig. 4.—Arteriogram (post mortem) of a normal control. Sub-branching more clearly visualized.

Fig. 5.—Arteriogram (in vitro) of a ligated control. Marked increase in number of collateral vessels.

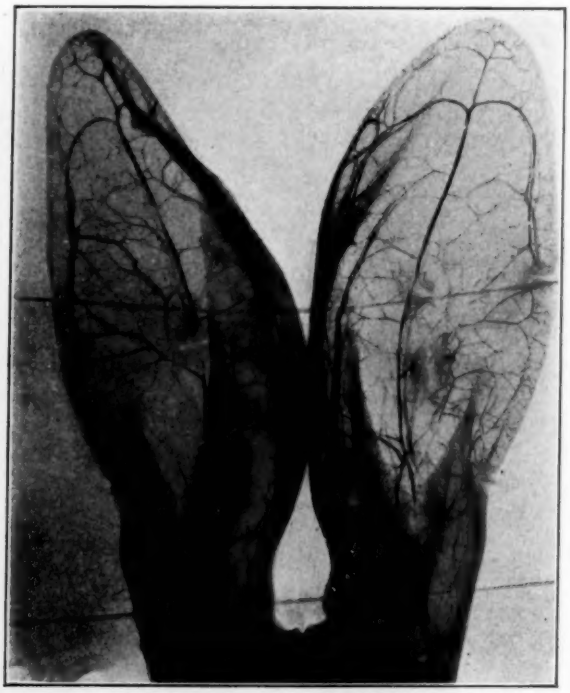

Fig. 6.—Arteriogram (post mortem) of a ligated control. Notice tortuosity, aimless ramifications, and irregular outline of the collateral vessels—also the bridging of the vascular obstruction by groups of small branches.

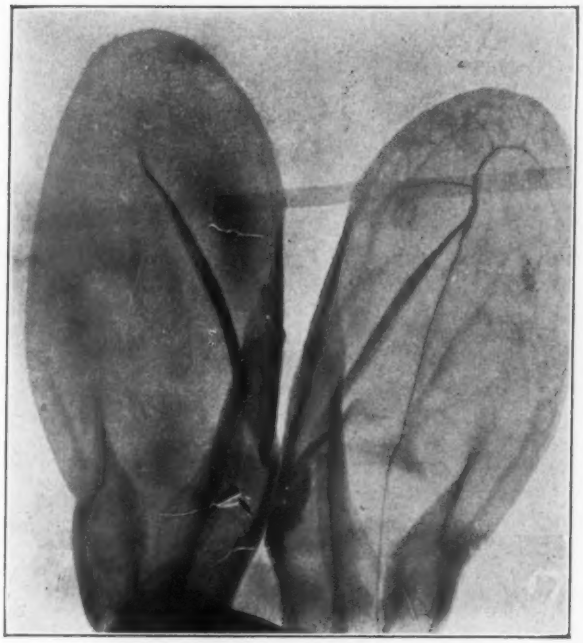

Fig. 7.—Arteriogram of ligated test animal. No vessels are visible on the treated side. Those on the untreated side are markedly narrowed, and but few of the smaller vessels are visible.

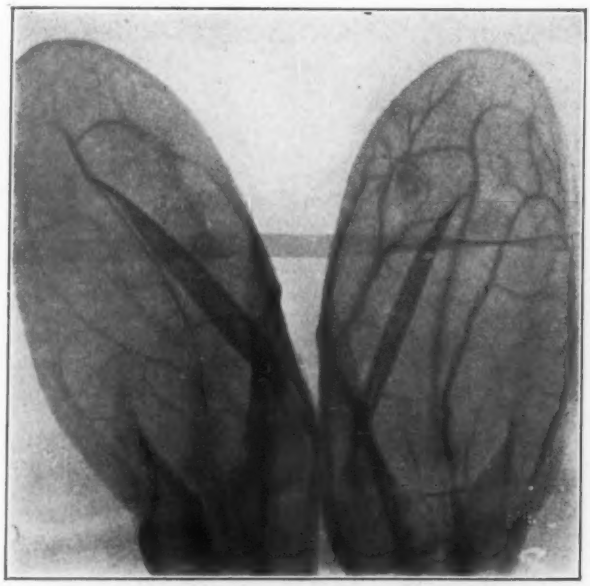

Fig. 8.—Ears of the same animal after exposure to a radiant lamp for five minutes. Vessels are beginning to appear on the treated side although they are still narrowed and very few collaterals are seen. Notice the marked dilatation on the untreated side and the increase in vascular branching.

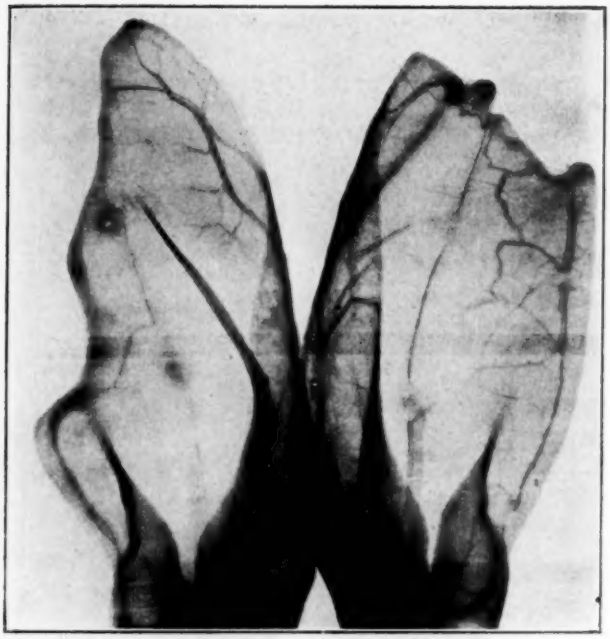

Fig. 9.—Arteriogram (in vitro) of a rabbit treated for several weeks by passive vascular exercise. The treated ear shows extensive necrosis and very few vessels. The untreated side shows a similar condition but to a lesser degree.

Fig. 10.—Arteriogram (post mortem) of the same rabbit. The collateral circulation is quite extensive and approximately equal on treated and untreated sides. In spite of this, necrosis has taken place in both ears.

outline. In the latter, the vessels are tortuous, ramify seemingly aimlessly and are markedly increased in number. This, as has been shown by Allen and Camp,[1] is characteristic of collateral circulation.

When the ligated ear is subjected to passive vascular exercise, several important changes are seen in the arteriographic plates. There is either no filling or only incomplete filling with thorotrast on the treated side. In other words, the lumina of the vessels are so narrowed that the injected material is unable to pass through. This is possibly the result of a vasospasm and may last for a period of several hours. As a matter of fact, even the other ear in the same animal exhibits a certain amount of narrowing of the vascular tree and a sparsity of collateral vessels. These changes may also be due to vasospasm, in all probability a reflex response (Fig. 7). The spasm or closure of the arteries can be overcome to a certain extent by the application of radiant heat just prior to arteriography. Fig. 8 shows this. Although the vessels on the treated side are still narrow and spastic and the collateral circulation still very sparse, yet the lumina have dilated sufficiently to admit the thorotrast. The vessels in the control ear in the same animal are widely dilated, very broad in caliber, and there is an abundance of secondary branches.

In the last group of animals which we subjected to ligation at different levels, we produced closure of the large vessels for almost three-quarters of their length. This meant that extensive collateral circulation would be needed to keep the ear alive. In the first rabbit, eight days after the start of passive vascular exercise and two weeks after ligation, the treated ear began to show an area of necrosis at the tip. Treatment was continued, however, and the area of necrosis became more extensive and finally began to involve the tip of the other ear. In the other test rabbit a similar condition began to appear in the treated ear about fifteen days after treatment, and then in the other and untreated ear about one week later. The control animal, which was also ligated in the same way but received no treatment, exhibited no such changes throughout the experiment. The gangrene kept spreading in the test animals in spite of treatment (Figs. 9 and 10). Post-mortem arteriography showed extensive collateral circulation present in both ears, both on the treated and on the untreated sides.

DISCUSSION AND SUMMARY

In our rabbits, simple ligation of the ear vessels proved to be a potent enough stimulus for the development of collateral circulation. Arteriographic studies on the living animal show that extensive branching occurs within a few days. In the human being an analogous condition occurs after acute closure due either to thrombosis or embolism of a large artery. If the collateral circulation develops with sufficient rapidity and to sufficient extent, the tissue involved will be saved. This

occurs with some frequency even without therapy, and makes one feel a trifle skeptical of the brilliant therapeutic results first recorded with suction-pressure treatment. As a matter of fact, the literature in the past year is of a rather equivocal nature, some authorities going so far as to state that passive vascular exercise will "not produce results which have not been produced by simpler methods," and that "when good results do not follow other measures, passive vascular exercise is usually valueless."[2, 3]

In these experiments, which of course were done on rabbits and not on human beings, we can say with certainty that passive vascular exercise is not only superfluous, but harmful. It produces cyanosis and vasospasm which persist for hours; and as treatment is continued, the constant deprivation of the tissues of their blood produces an anoxemia which results in necrosis. It must be emphasized that this sequence of events progresses rapidly in spite of treatment and in face of an abundance of collateral vessels.

NOTE.—I wish to thank Dr. Karl Harpuder, attending physical therapist to the Montefiore Hospital, whose guidance and assistance made possible these experiments.

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COMPLETE AURICULOVENTRICULAR BLOCK AND AURICULAR FLUTTER WITH OBSERVATIONS OF THE EFFECT OF QUINIDINE SULFATE*

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COMPLETE auriculoventricular block occurs frequently but it is not often associated with auricular flutter. A search of the literature reveals only 29 authentic cases. The comparative rarity of this condition and the observation of some unusual findings following treatment with quinidine sulfate are the reasons for this report.

The first reliable description of A-V dissociation accompanied by auricular flutter, was made by Jolly and Ritchie[1] in 1911; electrocardiograms and venous pulse tracings were shown. Hertz and Goodhart[2] in 1909 reported a young girl with auricular flutter in whom the ventricular rate fell to 44, after digitalis was administered; no electrocardiograms were made. Keating and Hajek[7] made the first reports in this country. Subsequently, Willius,[11] Strauss,[12] Gager,[17] and Parsonnet and Parent[20] published similar cases. Recently Routier[26] described two cases and summarized those previously recorded.

A survey of these cases (Table I) suggests classification into three types: (1) auricular flutter developing complete block after digitalis; (2) complete block developing flutter when given atropine, digitalis, and in one case after the advent of hyperthyroidism; and (3) the spontaneous occurrence of block and flutter. Our patient was of the last type and probably was first afflicted with heart-block which was subsequently complicated by auricular flutter for no apparent reason.

Only four of the 29 cases reported occurred in females, a somewhat smaller percentage than is found in heart-block alone. The ages varied between thirteen and seventy-four years, with 66 per cent in the sixth and seventh decades. The etiological factors were those characteristic of uncomplicated A-V block, namely, arteriosclerosis and coronary disease in most instances, with three cases of syphilitic heart disease and one each of rheumatic heart disease, congenital heart disease, and thyrotoxicosis. Of the 29 cases, in only eight was the auricular flutter rhythm restored to sinus control, five with quinidine, two with digitalis, and one following thyroidectomy. Quinidine failed to restore the sinus auricular control in one case where it was tried. A summary of the published cases is given in Table I.

*From the Department of Medicine, New York Post-Graduate Medical School and Hospital.

TABLE I

SUMMARY OF REPORTED CASES OF COMBINED COMPLETE HEART-BLOCK AND AURICULAR FLUTTER

AUTHOR	SEX	AGE	AURICULAR	VENTRICULAR	SIGNS	ELECTROCARDIOGRAM	REMARKS
Jolly and Ritchie, 1910	M	61	273	35		Flutter seen Leads II and III. Left axis deviation	Syncope five yr., A-V 60/31. Flutter after atropine. Persisted.
Hay, 1913	M	62	260	31	Systolic at apex, B.P. 170/90	Electrocardiogram—venous tracing	Flutter 10 yr., irregular ventricular rate, 87; after digitalis ventricular, 31 with persistent flutter.
Donzelot and Pezzi, 1914	M	62	300	37	B.P. 170/100; sharp first tone at aortic area	Flutter seen Leads II and III	Slow pulse two yr. Syncope one yr.
Martinez, 1916 Case 4	M	52	150	40	Cardiac insufficiency	No electrocardiogram; diagnosis by cardiogram	Cardiorenal with adhesive pericarditis.
Case 5	M	37	250	30	Cyanosis, ascites, systolic at apex	Diagnosis by cardiogram. Electrocardiogram not good	Cardiac insufficiency for five mo. Autopsy; septal defect with sclerosis of bundle of His.
Case 12	M	13	135	34	Cyanosis—systolic at apex	No electrocardiogram; flutter on cardiogram	Three mo. of syncope before death. Autopsy; degeneration of myocardium and bundle of His.
Goteling, Vinnis, 1920	M	68	250	40	B.P. 285/125; systolic at apex	No electrocardiogram. Venous tracing	Bradycardia—auricular 70, ventricular 35; flutter developed for eighteen mo. without symptoms after digitalis.
Arrillaga and Waldorf, 1921	M	42	225	25	Aortic insufficiency, B.P. 140/50	Flutter seen Lead II. Also bundle-branch block	Syncope for five mo. Atropine no effect. Adrenalin increased ventricular to 120.
Keating and Hajek, 1922	F	53	360	30		Flutter shown Lead II	Syncope, tachycardia then flutter with A-V block. Later sinus auricular rhythm and finally alternate flutter and fibrillation.

TABLE I—CONT'D

Gallemaerts, 1923	M	62				Bradycardia and flutter	Quinidine restored sinus rhythm.
Wiltshire, 1923	M	63	240	50	Coronary occlusion	Flutter seen Lead II	80 syncopal attacks daily auricular rate 100; ventricular 22, then ventricular pauses with auricular rate 160-240.
Hall, 1924	M	62	250	42	Bundle-branch block	Flutter with complete A-V block	Syncope for several years. Then developed flutter.
Willius, 1927	M	50	236	36	B.P. 160/95; arteriosclerosis; heart disease	Flutter Leads II and III. Left axis deviation	Pulse slow five yr., then developed flutter. No improvement on quinidine.
Henderson and Rennie, 1927	M	73	283	32	B.P. 165/80; no syphilis	Flutter in Leads II and III. Left axis deviation.	No improvement with atropine; died three mo.
Strauss, 1927	M	39	340	42	B.P. 135/70-96/60; thyroid adenoma	Flutter in all leads	Complete block. Developed hyperthyroidism and flutter; restoration of auricular sinus rhythm after thyroidectomy.
Parkinson and Bedford, 1927	M	74	270	35	Myocarditis. Systolic at apex	No electrocardiogram. Flutter on phlebogram	Digitalis produced auricular fibrillation then restoration of sinus rhythm with persistent block.
Lian and Viau, 1930	M	51	272	36	Syphilis. A-V block for 25 years	Flutter in Leads II and III	Digitalis restored sinus auricular control and A-V block persisted.
Gager, 1931	M	70	274	44	Arteriosclerotic; B.P. 122/78	Flutter Leads II and III. Left axis deviation	No response to digitalis; quinidine gr. 6 restored sinus rhythm with first stage A-V block.
Bosco and Vega, 1931	M	66	260	30	B.P. 180/120; cardiac insufficiency	Flutter Leads II and III	Flutter for two yr.
Ramos, 1932	M	40	300	30	B.P. 120/50; cardiac insufficiency	Flutter Leads II and III. Bundle-branch block	Cardiac insufficiency for two yr. Autopsy: lesions of both bundles.

TABLE I—CONT'D

AUTHOR	SEX	AGE	AURICULAR	VENTRICULAR	SIGNS	ELECTROCARDIOGRAM	REMARKS
Parsonnet and Parent, 1933	M	60	230 340	38	B.P. 150/60; coronary occlusion	Flutter Leads II and III. Left axis deviation, and later, right	Coronary occlusion three mo. previous; slow pulse some years; carcinoma of abdomen.
Braun Menendez, Case 1	M	56	206	40	Myocarditis. Syphilis	Flutter Leads II and III. Bundle-branch block	Syphilis at 27. Dyspnea since 45.
1934—Case 2	F	60	250	29	B.P. 188/132; systolic at apex	Flutter Leads II and III. Left axis deviation	One yr. syncope and dyspnea; no carotid sinus effect.
Bizzozero, 1935	F	39	240	30	Rheumatic mitral	Flutter Leads II and III	Atropine sulfate produced flutter in complete heart-block; amyl nitrite no effect.
Van Dooren, 1935	M	58	330	43	B.P. 190/60; aortitis; systolic at base	Lead II shown	Quinidine restored sinus auricular control. Block persisted with syncope.
Soulie, Cattan, and Bachman, 1936	F	66	200 280	30	B.P. 280/150; arteriosclerotic	Left axis deviation	After atropine developed slow flutter but had had paroxysms of slow flutter.
Routier, 1936 Case 1	M	66	360	30	B.P. 260/100; arteriosclerotic	Flutter Leads II and III. Delay QRS	Syncope and slow pulse two yr. Flutter eight mo. return sinus auricular control.
Case 2	M	52	190	36	B.P. 170/90; myocarditis	Flutter Leads II and III. Left axis deviation	Angina on effort for eight mo.
Authors' case	M	67	270	30	B.P. 178/62; arteriosclerotic; cardiac insufficiency	Flutter Leads II and III. Left axis deviation	Restoration of sinus auricular control with quinidine, temporary first stage block, later complete A-V block.

CASE REPORT

Italian, male, aged sixty-six years, formerly a restaurateur, complained of shortness of breath and weakness of two months' duration; a physician had advised him that he had "heart trouble." There was no history of previous illness. Two years previous he saw a doctor because of a "cold" and was told that his liver was enlarged. Nothing was said about his pulse and no medication was given.

Two months before admission, he had undergone considerable nervous strain and at that time he first noted a slow pulse. He suffered from progressive shortness of breath, palpitation, and dizziness. Because of these symptoms he was forced to sell his business one month before we saw him. More recently there had occurred some swelling of the ankles, loss of appetite, and epigastric discomfort after eating starchy food. He had lost twenty pounds by dieting during the past year. Otherwise the history was negative.

Physical Examination.—Revealed a rather obese male (25 lb. overweight for height and age); weight 190 lb.; height 5 ft. 8 in.; with evident respiratory distress; skin showed a slightly yellowish tinge; the mucous membranes were slightly cyanotic; eyes were negative except for subicteric sclerae; the pulse was 36, and

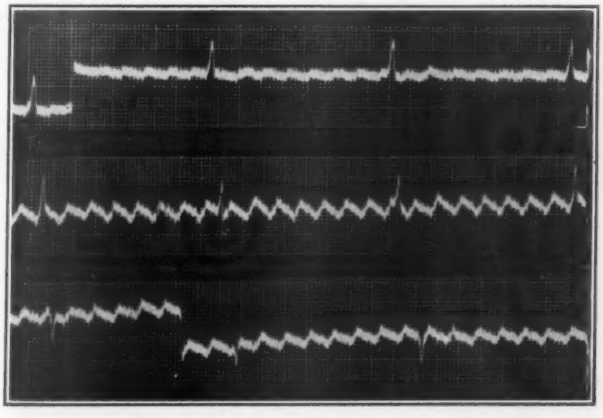

Fig. 1.—Auricular flutter, rate 270; complete heart-block; ventricular rate 36; tracing made before any treatment was given.

regular; the blood pressure was 178/62; there was slight distention of the jugular veins but no abnormal pulsation was observed; examination of the heart revealed diffuse enlargement which showed by the orthodiagram an M.R. of 7.5 cm. and an M.L. of 11 cm.; the heart tones were distant and muffled, with a systolic and a diastolic murmur at the apex, aortic area, and in the third interspace to the left of the sternum; the lungs showed emphysema but there were no signs of congestion or of fluid in the pleural spaces; the abdomen was negative except for the liver which was five cm. below the costal margin but not tender or pulsating; there was slight edema of the ankles.

Laboratory Tests.—Hemoglobin, 95 per cent; erythrocytes, 4,800,000; leucocytes, 4,200; with a differential count of: neutrophiles, 45 per cent; lymphocytes, 48 per cent; eosinophiles, 3 per cent; and myelocytes, 2 per cent. Urine: specific gravity 1.020; protein graded three plus to a slight trace in several specimens; a few hyaline casts and 30 leucocytes to the high-power field. Wassermann reaction: negative.

The fluoroscopic examination revealed slowly beating ventricles and a moderate globular enlargement of the heart; flutter of the auricles was not visualized. The electrocardiogram at this time demonstrated an auricular flutter with an auricular rate of 270 and a complete A-V dissociation with a ventricular rate of 36 (Fig. 1).

Clinical Course.—The patient was hospitalized and his progress followed with daily electrocardiograms. During hospitalization the weight dropped to 171 lb., a loss of 19 lb. Salyrgan 1 c.c. by intramuscular injection was used on two occasions. Digitalis, 7½ grains total, was given on the second and third day in the hospital. The digitalis was then discontinued and on the fifth day, quinidine sulfate was administered. Quinidine sulfate was given to tolerance on several occasions; October 16, the fifth hospital day, he received 31 grains of quinidine sulfate, and on the following day, 36 grains, when he developed nausea and gastric distress; at this time the pulse rose to 40 and an electrocardiogram showed a persistent flutter with an auricular rate of 130 (Fig. 2*A*). On the next day, October 18, quinidine sulfate, grains 18, was given when the patient again developed gastric distress and headache; the pulse rose to 58 on this day. The following day, October 19, quinidine sulfate, grains 24, was given; the pulse increased to 52 and an electrocardiogram showed a restoration of sinus rhythm with a first stage heart-block, the P-R interval being 0.72 seconds (Fig. 2*B*). Quinidine was continued for two more days in small doses and then withdrawn. In all, 109 grains of quinidine sulfate were given in four days, and 127 in six days. Electrocardiograms at various intervals for nearly seven

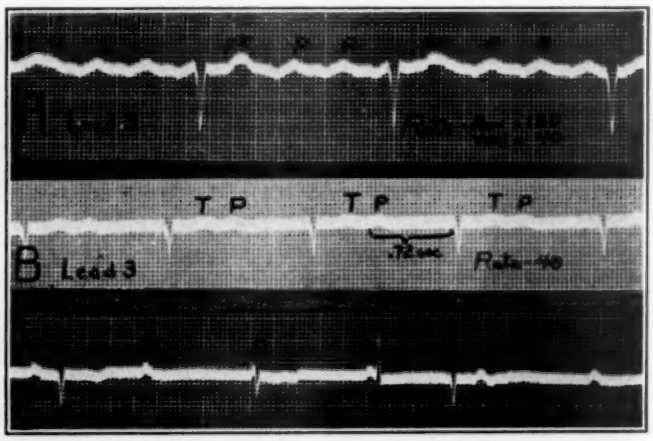

Fig. 2.—Showing response to quinidine. *A*, slow flutter after 67 grains of quinidine in two days; *B*, restoration of sinus rhythm with first stage heart-block after 109 grains of quinidine in four days; *C*, complete A-V dissociation which persisted after quinidine was discontinued.

months since that time, show a return of complete A-V dissociation with an auricular rate of 62 to 68 and a ventricular rate of 32 to 36 (Fig. 2*C*). Under the influence of quinidine there was a constant increase in pulse rate—on one occasion to 60 per minute. When the drug was withdrawn the pulse beat returned to the original rate, 36 to 38 (Fig. 2*C*). The blood pressure dropped during quinidine administration from 190/60 to 130/65, but after discontinuing the drug it rose to 166/60, at which level it has remained up to the present time.

COMMENT

This case of complete auriculoventricular block and auricular flutter developed several interesting changes on quinidine therapy. These were:

(1) Slowing of auricular flutter rate. (2) Increase in ventricular rate. (3) Restoration of sinus rhythm, with first stage block. (4) Return of complete A-V dissociation with normal auricular rate.

1. *Reduction of the auricular flutter rate* from 270 (Fig. 1) to 130 (Fig. 2*A*) was observed as an effect of quinidine, which is known to depress the conductivity of the auricles, ventricles, and bundle of His, and to lengthen the refractory period of the muscle. Levine[30] states that quinidine therapy may reduce the auricular rate while the flutter still persists, as was noted in this case (Fig. 2*A*). De Boer[28] explains the abolition of the circus movement by quinidine as a result of depression of conductivity, lowering rate of impulse formation, and lengthening of refractory period. He believes that an increase in the refractory period at first establishes the circus movement more firmly, but when the muscle is made more refractory by quinidine, the circus movement may then be blocked. This reasoning may apply in the present case as an explanation for the reduction in the auricular rate to 130 by quinidine (Fig. 2*A*), even though the flutter persisted, as well as the subsequent establishment of sinus rhythm with an auricular rate of 48 (Fig. 2*B*).

2. *Increase in ventricular rate* frequently results from quinidine administration. Levine[30] and White[29] observed that the ventricular rate may be either slower or accelerated by quinidine. White believes that when the rate of the auricular circus movement diminishes, the A-V conduction improves. This assumes the presence of a physiological block only, which usually pertains to auricular flutter. The improvement in A-V conduction occurs despite the fact that quinidine depresses the conductivity of impulses through the bundle of His. The increased ventricular rate was manifest on several occasions when the quinidine was given to the point of intoxication. An electrocardiogram was obtained on one occasion when the ventricular rate was 48 (although at one time the pulse increased to 60). Electrocardiographic tracing revealed a sinus rhythm with a first stage heart-block (Fig. 2*B*).

3. *Restoration of sinus rhythm with first stage block* in our patient was observed on only one occasion (Fig. 2*B*) and has been referred to in the previous paragraph. Complete auriculoventricular block recurred when the quinidine was discontinued (Fig. 2*C*). A persistent restoration of sinus rhythm was found by Schott,[4] Gallemaerts,[9] and Gager.[17] A first stage heart-block with a P-R interval of 0.24 second was reported by Gager;[17] the P-R interval shown in our tracings was 0.72 second (Fig. 2*B*); this is exceedingly long though Herrmann and Ashman[16] note one case with a P-R interval of 1.01 seconds. We feel that the restoration of sinus mechanism which occurred temporarily was due to marked slowing of the auricular rate to 48, which permitted impulses from the auricles to pass through the A-V node. This may be construed as evidence that there are conducting fibers present which are capable of transmitting impulses at a slow rate; however, when the auricular impulses reach the A-V node in rapid succession the node is not capable of accepting and transmitting them; it becomes refractory.

Thus when the auricular rate is that of flutter or even a normal rate of 70, the A-V dissociation is complete. We may, therefore, conclude that a physiological as well as an organic heart-block is present.

4. *Return of complete heart-block with normal auricular rate* occurred upon withdrawal of the quinidine sulfate and the subsequent return of the auricular rate to 70 (Fig. 2*C*). This conduction mechanism defect has remained constant during a period of six months' observation, in which the ventricular rate is found to persist at 36 to 38, and the auricular rate at 68 to 70. Since there have been no syncopal attacks, no real effort has been made to increase the ventricular rate or to employ any medication designed to decrease the block. We have hesitated to use large doses of atropine inasmuch as the patients reported by Jolly and Ritchie,[1] Soulie,[25] and Bizzozero,[23] developed auricular flutter after atropine was given. These patients previously had complete heart-block with sinus auricular control. However, on one occasion a small dose of atropine sulfate, grain $\frac{1}{75}$ was given. Curiously at this time an

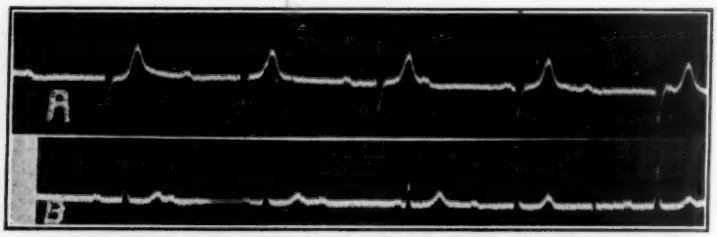

Fig. 3.—Showing the effect of 1/75 grain of atropine sulfate on ectopic ventricular focus *A*, before the injection of atropine; *B*, thirty minutes after injection.

electrocardiogram taken before administration of the drug indicated that the ventricles had assumed an ectopic focus (Fig. 3*B*). This degree of control by an ectopic focus has not been noted in several tracings made over a subsequent period of seven months. Thus the restoration of A-V rhythm control after atropine may have been coincidental. Levine states that atropine abolishes ectopic beats by increasing the heart rate through removal of the vagus effect. We observed no increase in ventricular rate despite the partial abolition of the ectopic focus.

SUMMARY

A case of spontaneous, complete auriculoventricular block associated with auricular flutter is reported. Treatment with quinidine reduced the auricular rate one-half and later resulted in restoration of the normal auricular rate with transient first stage heart-block and subsequent return to persistent, complete auriculoventricular block. Electrocardiograms after treatment with quinidine are shown and discussed. This combination of cardiac irregularities is rare and especially so

when, under treatment with quinidine, it goes through the stages of slow flutter, slow sinus rhythm with first stage heart-block and finally, return of complete heart-block.

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Department of Clinical Reports

A CASE OF TRICUSPID STENOSIS WITH ENORMOUS DILATATION OF THE RIGHT AURICLE*

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TRICUSPID stenosis can no longer be considered a very rare condition. About 250 cases have been reported in the literature[1] and it seems probable that there have been other cases diagnosed during life or at post-mortem examination which have not been reported.

There have been two cases at Barnes Hospital with a diagnosis of tricuspid stenosis established by autopsy findings from a total of 2,728 autopsies during the years 1914 to 1937. One was the case of a forty-one-year-old white woman with the usual symptoms of dyspnea, orthopnea, dependent edema, ascites, and cyanosis for about one year before death. There was a history of rheumatic fever when she was twenty-nine years old. At autopsy there was dilatation of all the chambers of the heart. The mitral and tricuspid orifices were each so narrowed that only the tip of the little finger could be admitted.

The other patient presented such unusual findings that it is considered worthwhile to report it in some detail.

CASE REPORT

C. A. S., a forty-three-year-old white woman, was admitted to Barnes Hospital four times and was observed over a period of more than two years. Her past history revealed neither major nor minor manifestations of rheumatic fever. She had a congenital kyphosis and scoliosis of an extreme degree. An attack of typhoid fever at the age of thirty-one years had been followed by an uneventful recovery. She married at the age of twenty and had two healthy children. During her first pregnancy a right-sided femoral hernia developed. A contralateral femoral hernia appeared during the second pregnancy four years later.

Symptoms of circulatory difficulty were first noted at the age of thirty-one following an operation for repair of the bilateral hernia. She recovered with difficulty from the anesthetic, and for the next two years suffered from frequent attacks of fainting. These finally disappeared, but after three years of apparent good health she noticed a gradually increasing swelling of her ankles and dyspnea on exertion. She was found to be pregnant and was aborted at seven months. Following this episode her face, legs, and abdomen started to swell, and other signs of cardiac failure made their appearance. Green pills were administered on several occasions by her physician, and once an abdominal paracentesis was performed which yielded

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two gallons of greenish fluid. Dyspnea, edema, and palpitation continued; later, orthopnea, cyanosis, and expectoration of bloody sputum were noted, and the patient entered Barnes Hospital in January, 1934, for treatment.

Physical examination revealed an undernourished woman sitting up in bed and severely dyspneic. She was intensely cyanotic. Her spine was deformed by an extreme degree of kyphosis and scoliosis, and the lower portion of the sternum was depressed. The superficial veins of the chest and abdomen were distended. The jugular veins were greatly distended, but did not pulsate. Both lung bases were dull to percussion and were filled with moist râles. The heart dullness extended to

Fig. 1.—Postero-anterior roentgenogram of the chest showing the extreme degree of right- and left-sided enlargement of the heart.

the axillary line in the fifth intercostal space on either side. Systolic and diastolic murmurs were heard over the entire precordium, loudest at the mitral area, and a diastolic thrill could be felt over the precordium and toward the left axilla. The second pulmonic sound was soft and faint. The auricles were in fibrillation. The blood pressure was 130/70. The liver was nodular, extended to the umbilicus, and did not pulsate. There was no ascites or pitting edema of the lower extremities. A large reducible femoral hernia was present on the left.

Shortly after admission the hernia became incarcerated and an immediate operation was performed. She almost expired during the course of the operation, but the subsequent post-operative course was uneventful. Following digitalization there was

considerable improvement in her condition, and she was discharged, to be followed in the heart clinic. Improvement, however, was only temporary, and during the next two years her symptoms became progressively worse. Persistent ascites was controlled to some extent by salyrgan. During this period she entered Barnes Hospital three times for symptomatic treatment. On one occasion one observer believed that the liver could be felt to pulsate, but this was not confirmed, and in general there was no change in the physical signs. She was admitted for the last time in February, 1936. Respiratory embarrassment was extreme, but the chest findings were essentially as before. The abdomen was greatly distended with fluid, and no organs could be felt. The patient was in such great distress that it was felt advisable to perform

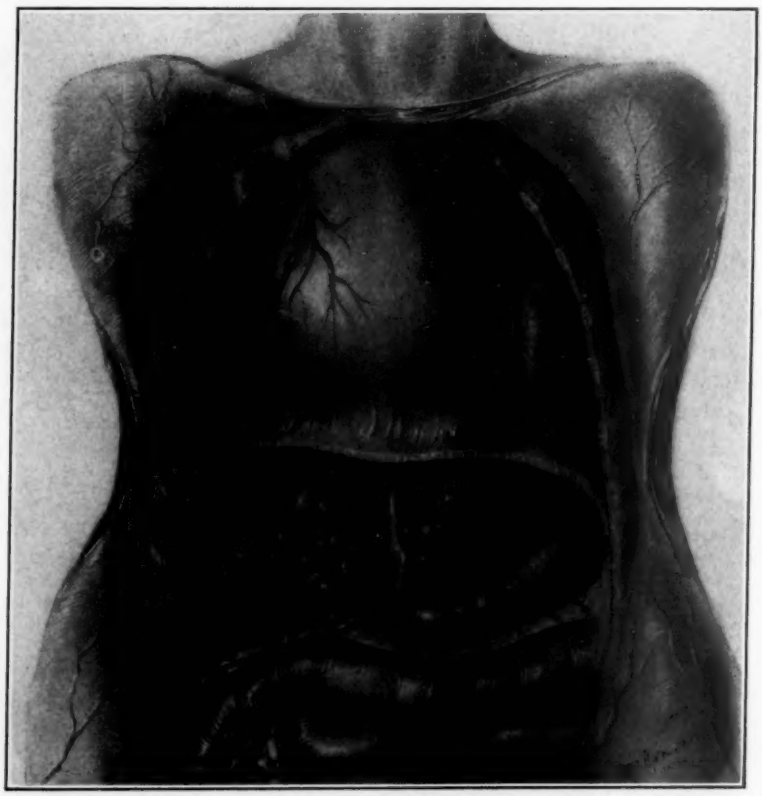

Fig. 2.—Drawing of the thoracic and abdominal cavities with the organs exposed in situ. The lungs are posterior to the heart.

a paracentesis. Fifty-five hundred cubic centimeters of very dark bloody fluid were withdrawn from the abdomen. The patient expired shortly afterward.

During the period when the patient was under observation the laboratory and fluoroscopic findings changed but little. There was a moderate anemia (red blood corpuscles numbered 3,500,000 with hemoglobin 67 per cent); the urine was negative and the blood Kahn was negative. The blood nonprotein nitrogen, calcium, and phosphorus were within normal limits. Electrocardiograms showed auricular fibrillation, slurring of the QRS complexes, right axis deviation, and a negative Dieuaide's sign. Roentgen ray films of the chest showed a heart shadow extending almost to the lateral chest wall on either side and increased lung markings. On fluoroscopy the right side of the heart could not be seen to pulsate; there was a clear posterior

mediastinal space. Venous pressures by direct measurement were 12 cm. and 20 cm. of water on two occasions. The velocity of blood flow, as determined by the decholin method, was 20 seconds and 28 seconds on two occasions. Because of the possibility that there was a massive pericardial effusion a needle was introduced 2 cm. anterior to the right mid-axillary line and 1 cm. into the thorax, and pure blood was withdrawn. Oxygen content determinations showed this to be venous, and established the fact that the needle had entered the right auricle.

Relevant post-mortem findings.—Post-mortem examination disclosed an emaciated middle-aged woman with pitting edema and reddish-brown discoloration of the lower extremities. There was an extreme scoliosis of the thoracic spine to the right. Two liters of blood-tinged fluid were found in the peritoneal cavity. All the vessels of the peritoneum were engorged. The pleural cavity contained no excess fluid and no

Fig. 3.—The endocardial surface of the right auricle with the stenotic tricuspid orifice.

adhesions. The pathological diagnoses were: (1) chronic rheumatic (?) endocarditis of the mitral and tricuspid valves with insufficiency and stenosis; (2) adherent pericardium over the right auricle only; (3) enormous dilatation of the right auricle; (4) scarring and hypertrophy of the muscle fibers of the right auricle; (5) slight dilatation and hypertrophy of the right ventricle; (6) partial pulmonary atelectasis (compression); (7) ascites and edema of the ankles; (8) congestion of the liver, spleen, and peritoneal tissues; (9) marked scarring of the liver; (10) scoliosis of the thoracic vertebrae; (11) slight aortic atherosclerosis.

Heart: The heart and pericardial sac occupied most of the chest cavity and completely hid the lungs from view. The pericardial sac was found to be adherent over the right auricle with the exception of the appendage and an area adjacent to it. There were no mediastinal or pleural adhesions, nor was the pericardium adherent over the other chambers of the heart. On removing the heart from the chest cavity the major part of it was seen to be right auricle. Its wall was about two-thirds its normal thickness, but it must have had a great increase in substance since

it was not strikingly thin in spite of its great size. There were smooth white plaques in the endocardium lining the auricular appendage which were probably old organized thrombi. The endocardium was somewhat thickened and opaque toward the edge of the tricuspid ring. The capacity of the right auricle was 2,150 c.c. The right ventricle was only a little larger than normal, and its wall was of about normal thickness. It had a capacity of about 100 c.c. The left auricle was neither dilated nor hypertrophied; its contents measured 95 to 100 c.c. The endocardium above the mitral valve was opaque, but there was no definite auricular patch of rheumatism. The left ventricle was of normal size. The tricuspid cusps were fused, forming a rounded opening with moderately thick and retracted edges which measured 7 cm. in circumference and were incapable of closing. The chordae tendinae were thickened. The mitral valve was thickened and retracted so that the division into cusps was no longer apparent. Its circumference was 5 cm. The circumferences of the

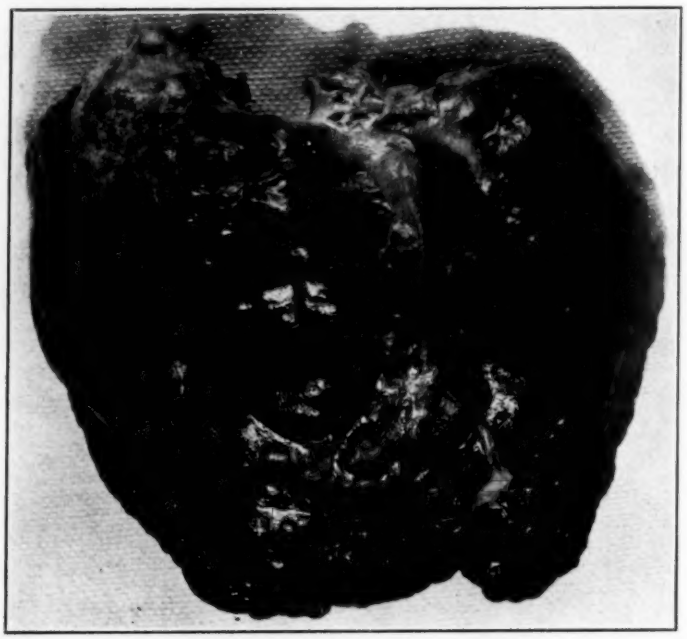

Fig. 4.—The small, atrophic liver with its irregularly nodular surface.

pulmonary and aortic valves were 10 cm. and 7.75 cm. respectively. They were normal in appearance. The heart weighed only 505 gm. in spite of the tremendous right auricle.

On microscopic examination the bundles of muscle fibers of the right auricle were greatly hypertrophied and were interspersed with vascular and cellular connective tissue. In some places there were only thin strands of interrupted hypertrophied fibers. The nuclei of the muscle fibers were large and hyperchromatic. There was a moderate hypertrophy of the muscle fibers of the right ventricle and left auricle and none of the left ventricle. No Aschoff bodies were seen.

Lungs: The lungs were compressed and lay posteriorly to the heart. There was a partial collapse of the lower lobes, especially of the left. They showed a surprisingly small amount of congestion. On section there were seen alternating areas of collapse and overdistention of the alveoli. Some of the partially collapsed areas showed a little blood in the alveoli. The pulmonary artery showed no intimal changes.

Liver: The liver was smaller than normal, weighing 1,285 gm. The surface was irregularly nodular, and variation in the size of the nodules was greater than is usual in cirrhosis. The capsule was somewhat thickened, and the cut surface was of a deep red color and firmer than normal, as if containing an excess of connective tissue. Although there were some areas which were more congested than others, they did not seem to correspond to the normal central portions of the lobules, but were larger and less regular in arrangement. Little normal lobulation was seen. On section lobules with normal relations to central veins were distinguishable. In these areas the periportal tissue contained scarcely more connective tissue than usual and a few wandering cells. The sinuses about the central veins were widened and the liver cells atrophied. Other zones, however, showed wide communicating bands of connective tissue containing small bile ducts, a few lymphocytes and plasma cells, and occasional hemorrhages. Many such zones connected with the thickened capsule.

Spine: There was a marked curvature to the right which extended from the fourth to the tenth thoracic vertebra, and there was a maximum deviation of 6.5 cm. from the midline. Microscopic section offered no clue as to the etiology of the curvature.

DISCUSSION

The diagnosis of tricuspid stenosis was not made in this case before death. It was recognized, however, that the patient had an enormously distended right auricle, together with a left auricle which was little or not at all dilated. The aspiration of venous blood from the right chest and the persistently clear posterior mediastinal space established this. Therefore, only those conditions which might lead to isolated hypertrophy of the right side of the heart were considered. Although Broadbent's sign and diaphragmatic tug were absent, the question of mediastinopericarditis was raised on the basis of fixation of the cardiac shadow, a negative Dieuaide's sign, the presence of periapical recession about the apex, and persistence of ascites after disappearance of edema of the lower extremities following digitalization. A patent foramen ovale in the presence of mitral stenosis was considered in view of the enormous size of the right auricle and the presence of another congenital defect, viz., the curvature of the spine. Against this was the soft quality of the pulmonic second sound and the long-standing cyanosis. Although tricuspid stenosis was considered, the failure to identify a diastolic thrill and murmur localized at the tricuspid area or other strictly characteristic signs prohibited a definite diagnosis.

Tricuspid stenosis may be either a congenital defect or the result of rheumatic heart disease. In the majority of cases, however, it is due to the latter[2] even in the absence of a history of frank rheumatic heart disease. Often enough one can elicit a history of "minor rheumatic manifestations" described by Kaiser.[3] In the case reported above there is considerable room for speculation in regard to the cause of the heart lesions. The absence of a history of rheumatic manifestations of any sort; the presence of a congenital spinal deformity, a condition occasionally associated with congenital heart lesions; and the smooth and rounded appearance of the tricuspid valve instead of the irregular

cicatrization characteristic of endocarditis[1] are in favor of the congenital origin of the condition. On the other hand, the absence of a deficient auricular septum (an almost inevitable consequence of congenital right heart valvular obstruction[4]) and the appearance of cyanosis in adult life rather than in infancy offer almost unequivocal evidence that the cardiac defects were acquired.

The possibility that the spinal deformity acted as a contributing cause of the changes in the heart is difficult to evaluate. In cases of extreme kyphoscoliosis there is often diminution of the pulmonary blood stream and compression of the great vessels. As a result of this considerable strain is thrown on the ventricles, which become secondarily hypertrophied and dilated.[5] In view of the fact that in this case the changes in the ventricular myocardium were comparatively insignificant, one may conclude that the effects of the chest deformity on the heart were minimal.

Patients with tricuspid stenosis not uncommonly live for many years after the appearance of evidences of congestive failure,[6] a fact well exemplified by this patient who suffered for ten years with an almost continual state of cardiac decompensation. In spite of an extreme mitral stenosis the left auricle was of normal size, and one must believe that the left heart was spared at the expense of the right and that the right auricle acted as a reservoir from which blood was not admitted to the right ventricle and left heart with sufficient rapidity to cause hypertrophy or dilatation. For this reason the pressure in the pulmonary vessels was low, the second pulmonic sound was soft and faint, and pulmonary congestion was not a prominent feature. The increased pressure was apparent chiefly in the peripheral venous circulation and symptoms of extreme edema and ascites were prominent throughout the course of the disease. The circulation was slowed sufficiently to result in intense cyanosis. Thus, patients with this condition have a longer life expectancy than those with uncomplicated mitral stenosis because the heart is relieved of the strain at the expense of the peripheral vascular system.

Tricuspid stenosis most frequently occurs in association with mitral stenosis.[7] A study of the reported cases in which these two lesions were associated reveals a striking diversity in the state of the heart chambers in the presence of a certain uniformity of the valvular lesions. For example, in most cases there is some dilatation of the right auricle, but often all the chambers show dilatation and hypertrophy. Sometimes the left side of the heart is more greatly affected than the right, sometimes the right more than the left. Rarely the right auricle alone is dilated[2] (case 1), or the size of the chambers is essentially normal.[1] Griffith[8] has pointed out that isolated stenosis of the tricuspid valve is extremely rare, and remarks that in view of the fact that mitral stenosis often occurs alone one is led to the inference that tricuspid stenosis

is secondary to mitral stenosis. It seems logical to conclude, therefore, that the effect of the stenoses on the heart as a whole depends not only on the degree of stenosis, but especially on the time interval that elapses between the mitral and tricuspid affections. Thus, for example, when the left auricle is greatly dilated, it might be inferred that the mitral valve was narrowed for a considerable period of time before the tricuspid. On the other hand, when the right auricle is especially dilated, it can only mean that the left side of the heart has been spared by the tricuspid lesion and that the mitral lesion antedated the tricuspid by only a short interval of time.

In the case reported above it seems likely that tricuspid stenosis appeared early in the course of the endocarditic process with a consequent result of a huge dilatation of the right auricle together with approximately normal-sized left auricle and ventricle. The great enlargement of the right auricle was undoubtedly enhanced by the long-standing fibrillation. The strain of the venous column of blood was thrown entirely on the passive walls of the right auricle which were unable to contribute to the forcing of the blood through the auriculoventricular opening.

The liver presented a complex and somewhat confused picture. Grossly it showed the typical picture of the so-called "nutmeg liver" resulting from long-continued stasis with collapse and fibrosis. Microscopic examination revealed a striking degree of degeneration and connective tissue infiltration, which corresponded to the final stage of "collapse fibrosis" described by Lambert and Allison.[9] It is noteworthy that in spite of the protracted course of the disease and the advanced pathological alterations, the changes were not diffuse throughout the liver, but were much more prominent in some areas than in others. This variability has been noted by Lambert and Allison and other workers. However, in this case the connective tissue increase was not confined to the regions around the center of the lobules, but irregularly involved the portal spaces. Here and there the connective tissue of Glisson's capsule surrounded whole groups of lobules. Such a picture has been described as occasionally occurring in the "cardiac liver,"[10] but it is apparently not characteristic of this condition, and leaves some room for doubt whether all the changes can be ascribed to chronic passive congestion, or whether, as has been observed in rare cases, some of the changes were the result of a true portal cirrhosis.

SUMMARY

A case of mitral and tricuspid stenosis has been described. Remarkable was the huge dilatation of the right auricle while the other chambers of the heart were of approximately normal size. The probable cause of this isolated dilatation has been discussed. Remarkable, too, was the advanced collapse and fibrosis of the liver, which may have been

due entirely to long-continued chronic passive congestion or possibly to a combination of stasis and a true portal cirrhosis.

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BUNDLE-BRANCH BLOCK IN A NORMAL YOUNG MAN

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EPPINGER and Rothberger[6] were the first to demonstrate the characteristic electrocardiographic curves after section of a bundle-branch in dogs. Cohn and Lewis[3] showed the pathological changes in the hearts of four persons who during life had the characteristic curves; two of these hearts showed a lesion causing a disappearance of the bundle fibres: and of the other two one showed increased fibrous tissue in the ventricular septum, while the other had intact main stem and branches with obliteration of the smaller branches by connective tissue.

Bach[1] has subdivided the clinical cases into three groups according to their etiology, cardiovascular degeneration, syphilis, and rheumatism.

Von Deesten and Dolganos[18] add another group in which the curve is of an atypical variety and the prognosis is good.

More recently Wood and his associates[22] have published a follow-up of 64 similar cases.

Wolffe, Parkinson, and White[21] describe a fifth group occurring in healthy young people prone to paroxysmal tachycardia. They give reference to a case of Wedd's of a similar kind; Holzmann and Scherf[10] described two similar cases; while Pezzi[15] recorded three more under the heading "permanent paraseptal rhythm." Chen Lang Tung[2] described another similar case under the heading "functional bundle-branch block." Sigler[17] wrote of functional bundle-branch block paradoxically relieved by vagal stimulation.

It is probably to this fifth group that the case reported here belongs.

R. R., aged twenty-one years, apparently in perfect health, applied for employment. In the course of routine medical examination an electrocardiogram showed bundle-branch block of the uncommon variety (left bundle-branch block, old terminology) with a short P-R interval. Careful questioning on two occasions revealed a history of chickenpox at the age of three years and measles at the age of five years. There was no history of rheumatic fever, chorea, growing pains, scarlet fever, or venereal disease. There had never been any shortness of breath or symptoms to suggest paroxysmal tachycardia. He was a moderate smoker.

On examination he was well built and healthy looking. The heart was normal in size and shape clinically and radiologically. The heart sounds were normal. Blood pressure was 140/80, the arteries were soft. The pulse frequency varied between 80 and 90 per minute, sinus arrhythmia was present. The remainder of the clinical examination was negative. The effort test was very good, and blood Wassermann was negative.

The electrocardiogram showed the following time relationships:

P-T 0.5 second (Leads I, II, and III)
P-Q 0.1 to 0.12 second
P-S 0.24 to 0.28 second,

compared with the time relationships of a normal control

P-T 0.48 second
P-Q 0.18 second
P-S 0.22 to 0.24 second

compared with a typical case of bundle-branch block

P-T 0.52 second
P-Q 0.22 second (+ or −)
P-S 0.26 to 0.28 second.

Considering the divergent views on the intraventricular block in these cases, the following tests were carried out: (1) Effect of deep breathing, (2) Pressure on the vagi, first right then left, (3) Exercise, (4) One-fiftieth of a grain of sodium trinitrini by mouth, (5) One-hundredth of a grain of atropine subcutaneously.

No change in the shape of the curve was noted in the first four tests. Forty minutes after the injection of atropine there was a change in the

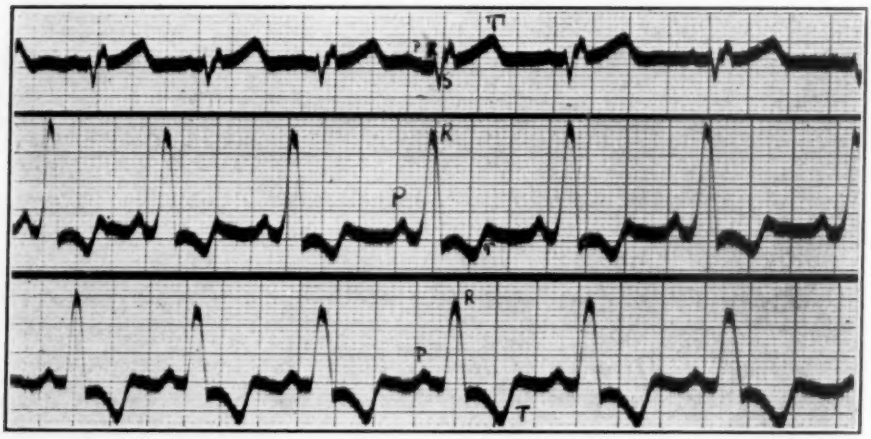

Fig. 1.—R. R., aged twenty-one years. Bundle-branch block; before atropine.

shape of the T-waves in Leads II and III, which became more marked in sixty minutes. Before giving atropine the T-wave was inverted in Lead II, with a slightly diphasic wave, and deeply inverted in Lead III; the atropine caused a more vertical T-wave in Lead II and a diphasic wave in Lead III; there was also a slight lengthening of the S-T period. There was no change in the P-R interval (which varied in different leads from 0.9 to 0.12 second) or of the QRS period which remained 0.12 second, the P-waves increased in amplitude.

It was not possible to repeat the experiment with larger doses of atropine as the young man went abroad.

DISCUSSION

Prognosis.—The significance of bundle-branch block is, according to King,[13] very grave regardless of etiology, though it appears best in those cases of rheumatic etiology. King showed that of 104 patients, 76 were

dead at an average of one year from the time of the discovery of the condition. He gives two years and eight months as the expectation of life in the rheumatic group.

Bach gives a slightly better prognosis for the cardiovascular degenerative group, describing cases of fourteen, nine, and seven years' duration. Graybiel and Sprague[8] record an average duration of one year and two months in 223 fatal cases out of 308 cases followed up.

Van Deesten and Dolganos in their atypical group (QRS prolonged, R in Lead I of moderate amplitude and short duration, S in Lead II prolonged and notched), show periods of eleven and one-half, eight, and two and one-half years, the patients being still alive. Wood and his associates gave similar findings.

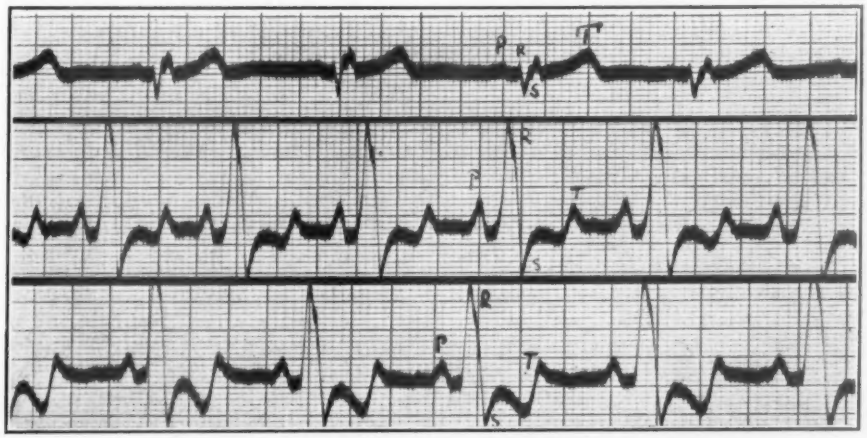

Fig. 2.—R. R., after atropine.

Wolffe, Parkinson, and White state of their particular group that there is no indication of heart disease, and record a case of fourteen years' observation, and no deaths in their series.

The case described here falls into the last group and has therefore a good prognosis as far as present knowledge can tell.

Mechanism of the Bundle-Branch Block.—Various views have been formulated on the mechanism of this form of bundle-branch block. There is no record of a post-mortem examination with careful histological research on a case of this kind.

Vagal tone has been considered to be the causative factor, and Wolffe, Parkinson, and White favor this view. They postulate a paradoxical vagal effect as the explanation of the shortened P-R interval, or in other words, release of vagal tone is accompanied by lengthening of the P-R interval. In their report of eleven cases they record that vagal compression in one case changed a normal type of curve to that of widened QRS and shortened P-R interval, while exercise in another case restored a normal curve which, with the person at rest, showed intra-

ventricular block. In two other cases intraventricular conduction was normal during attacks of paroxysmal tachycardia; there was no record of variation in the intraventricular conduction in four cases.

Wilson described a patient who, on taking a deep breath, changed a normal ventricular conduction into that characteristic of intraventricular block; the P-R interval also shortened from 0.17 second to 0.1 second.

Hering[9] recorded abnormal ventricular complexes during vagal stimulation in a dog, in which each abnormal ventricular complex was preceded by an auricular complex.

On the other hand Sigler[17] recorded a return to normal intraventricular conduction in two cases of bundle-branch block, one after thirty hops and the other after vagal compression. Also Gaskell[7] showed that the rate of conduction from auricle to ventricle may be depressed by vagal stimulation in animals, i.e., P-R interval increased; and Ritchie[16] found that compression of the vagus does not as a rule cause any depression of conductivity in the auriculoventricular bundle, although rarely compression of the right vagus may lengthen the auriculoventricular conduction time. No mention is made of decrease of auriculoventricular conduction time. Ritchie also found no change in the length of ventricular systole, with one exception when a ventricular beat lengthened from 0.35 second to 0.45 second.

Lewis and Master[14] found that 2:1 heart-block could be produced in the mammalian heart by vagal stimulation, but that the refractory period of the tissue concerned in auriculoventricular conduction is less influenced than that of auricular muscle by vagal stimulation.

Drury and Mackenzie[4] proved by their experiments that vagal stimulation in the dog has no influence on impulses spreading in the bundle branches or through ventricular muscle. They postulate that vagal stimulation may increase the gradient of decrement at higher levels (e.g., auriculoventricular bundle) or decrease the impulse strength at this higher level, then the impulse will be below normal strength when it arrives at the bundle branches. They state that a local condition constantly present and not connected with vagal stimulation may steepen the gradient more in one branch than the other so that the weakened impulse will be relatively more delayed in one branch than the other or even run to extinction.

In those conditions in which complete vagal heart block is present and the idioventricular beats are abnormal they feel that the more likely explanation is that impulses arise in the bundle above its bifurcation and are subject to decremental conduction rather than that they arise in a bundle branch.

Einthoven[5] described flattening and inversion of the T-waves in the dog during vagal compression, but no mention of change in the P-R or QRS intervals.

The experiment with atropine on the case described did not affect the P-R interval or the wide QRS wave, but did tend to elevate the T-waves. Vagus compression and exercise were without effect.

To sum up with regard to the vagal theory; Wolffe, Parkinson, and White, and Wilson and Hering, bring some experimental reasons in its favor, but it is difficult to correlate them with the generally accepted views of vagus function. Also in the case described apart from the change in the T-waves, after atropine injection, there was no evidence of vagal influence.

Pezzi believed that the abnormality of the ventricular complex was due to a paraseptal rhythm which would also explain the short P-R interval. The presence of ectopic ventricular beats in other cases, the vertical P-wave and the permanence as a rule of the condition, do not support his theory.

Holzmann and Scherf[10] postulate an abnormal path connecting the auricle and ventricle which misses the auricular and ventricular nodes. Wolferth and Wood[20] write that all the data so far obtained are in keeping with the possibility that an accessory pathway of auriculoventricular conduction (such as described by Kent between right auricle and right ventricle) could be responsible for the phenomena manifested by these cases. The anatomical evidence of this path is not, however, completely conclusive.

Measurements of P-T and P-S times in this tracing, in normal tracings, and in ordinary bundle-branch block tracings have been given for comparison as it has been suggested that there is no lengthening of the total P-T periods as in ordinary bundle-branch block.

It has been postulated that the QRS is prolonged as there is a premature contraction of one bundle due to the impulse passing down the bundle of Kent instead of in the auriculoventricular bundle with resulting shortening of the P-R interval.*

It is difficult to believe any of the functional theories and not to feel that there is probably a mechanical abnormality in the bundle-branch system due to a local nonprogressive lesion. The fact that normal intraventricular conduction may sometimes occur temporarily is not a contraindication to a lesion in the bundle. Hermann and Ashman described transient normal intraventricular conduction with lengthening of the P-R interval in the presence of apparently complete bundle-branch block in persons with gross disease of the heart: these periods of normal conduction tended to happen after rest. Baker brought about temporary disappearance of bundle-branch block by rest and also by administering oxygen to an old man with myocardial disease. In the case of the young man which I have investigated I feel that there is either an area of fibrosis interfering with one of the bundle branches or possibly a con-

*It should be noted that the P-R interval in this tracing is only slightly shortened (0.1 second).

genital abnormality in the bundle-branch conducting system, e.g. bundle of Kent. There is no evidence, at the moment, in his case of any variation in the ventricular conduction.

SUMMARY

A case of bundle-branch block with a slightly shortened P-R interval in a normal young man is described.

Electrocardiograms were taken after deep breathing, pressure on the vagi, exercise, and after giving sodium trinitrini by mouth, and showed no change.

Injection of one-hundredth of a grain of atropine subcutaneously tended to elevate the T-waves in Leads II and III.

References are made to numerous theories on the mechanism of bundle-branch block in normal persons and also to cases described by other authors.

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COMPLETE HEART-BLOCK IN ACUTE RHEUMATIC FEVER

Case Report

Alfred M. Wedd, M.D.
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COMPLETE heart-block is but rarely encountered in acute rheumatic fever. In 1932, Wedd[3] reported one case of transient block with complete recovery, and reviewed recent literature. Since then there have been a few isolated case reports. In that paper[3] two instances of partial block in acute rheumatic fever were also described, and because of changes which occurred during the course of the disease it was suggested that such block might be on a functional basis and not necessarily dependent on structural change. Atropine was not tried in those cases, but later I cited an example of reduction by atropine in the degree of high-grade partial block which had followed a severe throat infection.[4] Recently Bruenn[1] has reported transient diminution by atropine of the prolonged conduction time in 19 of 22 cases of acute rheumatic fever in which the test was made, and he concluded that the conduction impairment of that disease was due, at least in part, to increased vagal tone. Such observations are of considerable interest in relation to those of Gross and Fried,[2] who found minimal changes in the conduction system in acute rheumatic fever. Vascular changes appeared to them more frequent and more conspicuous than exudative. It is possible that the relief of block by atropine might be partly due to increased coronary flow, such as occurs in the experimental animal, although the dilator action of atropine is seldom marked, and when present is probably part of vagal release. In a case of transient complete block which followed thrombosis of the right coronary artery, block did cease for a short period four to six minutes after the subcutaneous injection of 2 mg. of atropine, but this effect probably resulted from the fall in auricular rate from 75 to 65 beats per minute during the early stimulating phase of atropine action; when the auricular rate rose to 112 per minute a 2:1 block was established. The atropine response in the present case seems comparable to the termination by that drug of complete block that has been produced by digitalis,[5] and lends further support to the idea that a vagal factor is largely responsible for such block. Since this patient was of an unusually placid temperament and syncopal attacks and block occurred only after physical strain, it would seem that in this case the origin of heightened vagal tone was in the heart, and not in the medulla, as Bruenn argued for his patients. The therapeutic importance of con-

sidering a functional factor in the heart block of acute rheumatic fever, and the possibility of its relief by atropine, is brought out in the following case history.

The patient, an unmarried woman forty-one years of age, was admitted to the hospital July 31, 1936. At the age of twenty-one years she had diphtheria. Recurrent attacks of tonsillitis had occurred previous to tonsillectomy in 1929. Several teeth had been extracted during recent years because of hypertrophic arthritis which had gradually developed in several finger joints. On July 4, she had gone swimming. She stated that she remained too long in the water and became chilled. Two days later she experienced severe pain in the right elbow, but thought it had resulted from a bruise. Two days after that, because of continued pain, she consulted an osteopath, who found her temperature to be 103° F. The elbow remained painful for about one week. During the middle of July there was pain and swelling in the right ankle joint. An ointment had been applied to the painful joints, and there were no signs of acute arthritis at the time of admission to the hospital. Throughout the entire month the patient frequently experienced profuse sweating, especially at night, and she knew that fever had been present at least part of the day. However, she had continued her work as a telephone operator up to the time she came to the hospital. For two days before giving up she noticed unusual shortness of breath on climbing a single flight of stairs. She also described throbbing of the heart, a feeling of weakness in the heart, and at times burning beneath the sternum. Three days before admission to hospital while on a long motor trip she complained of aching in the precordial region. During the last week of July giddiness and faintness occurred after going up stairs. On the evening of July 30, she consulted her local physician and while in his office fainted. The next morning she had another syncopal attack and was then sent to the hospital. No drugs had been administered.

When first seen the woman appeared critically ill. She was vomiting, and the skin was pale, cold, and wet. The heart sounds were of poor quality. The rate was about 50 per minute but the rhythm was irregular, with long intervals between some of the beats. The following morning she was quite comfortable. The only significant abnormal findings were in the heart. The heart appeared slightly enlarged to the left. A gallop rhythm was heard, and at the apex a faint systolic murmur. The rhythm was regular, with a rate of 96 per minute. The systolic blood pressure was 108 and the diastolic, 72. The temperature was normal. Blood examination showed a mild secondary anemia, and a leucocyte count of 16,800, of which 90 per cent were neutrophiles. In the urine there was a strong trace of albumin, hyaline, and finely granular casts, and a few erythrocytes.

The patient continued free from symptoms until the afternoon of August 3, when following an enema a series of syncopal attacks occurred. Three generalized convulsive seizures were observed. After vomiting, a cold sweat of extreme degree appeared. Only an occasional heart sound could be heard; the radial pulse was imperceptible, and the blood pressure was not measureable. She was very pale, but there was no cyanosis. There was no prolonged loss of consciousness, and dyspnea was strikingly absent. That death was imminent was the opinion of all who saw her, and of the patient herself. Epinephrine, first 0.3 c.c. of 1-1000 solution, and five minutes later, 0.5 c.c. was injected intramuscularly without any beneficial effect, although the drug apparently caused some auricular slowing and an occasional ventricular response to an auricular impulse. Ten minutes after the second epinephrine injection, 2 mg. of atropine were injected deep into a deltoid muscle. After four minutes ventricular beats began to occur more frequently and an occasional beat came through to the wrist. Eleven minutes after atropine the cardiac mechanism became normal, and it remained so. The shock-like state passed off in about two hours.

The remainder of the patient's stay in the hospital was uneventful. No further syncopal attacks occurred, nor were there any other cardiac symptoms. The morning following the severe attack the heart rate was 64 per minute, and it continued within normal range. A sinus arrhythmia was often present. The apical murmur disappeared after the first few days. The blood pressure remained low, systolic 86

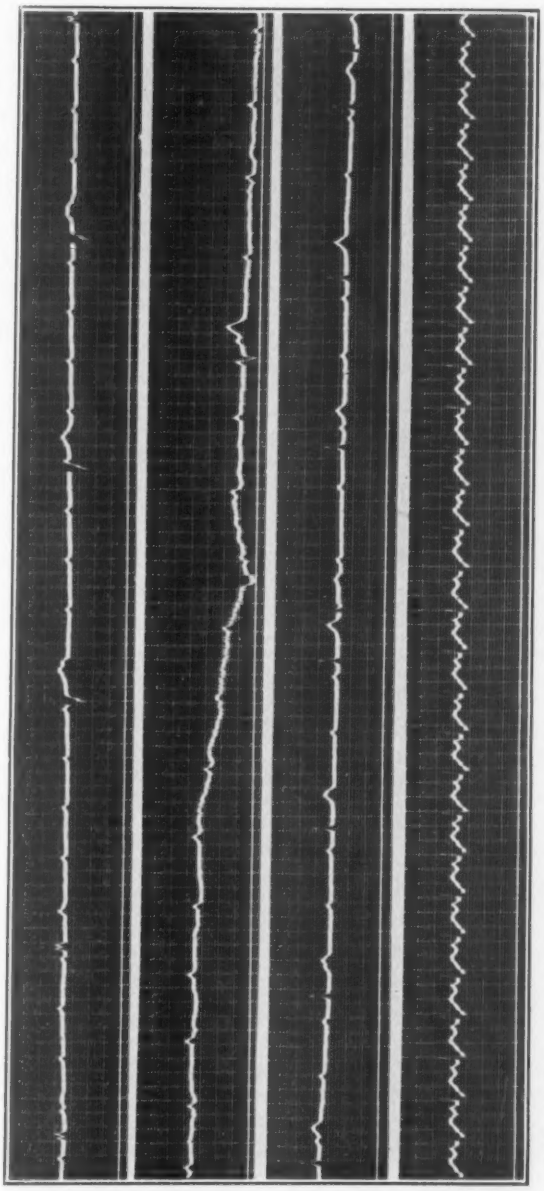

Fig. 1.—Line 1. Part of first record. Line 2. Shortly after the preceding, and during a mild convulsion; one recorded ventricular beat in 20 seconds. Line 3. After the second epinephrine injection. Line 4. 15 minutes after atropine. Time marker, 0.18 sec.

to 106, diastolic, 60 to 80. Fever ceased promptly under salicylate medication. Fluoroscopic examination on September 14 showed slight uniform enlargement of the heart, which was transversely placed. All electrocardiograms taken after the period of complete dissociation have shown intraventricular block, but a normal P-R interval.

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3. Wedd, A. M.: Complete Heart Block in a Case of Acute Rheumatic Fever. Partial Heart Block in Acute Rheumatic Fever, Clifton Med. Bull. **18:** 63, 1932.
4. Wedd, A. M.: Syncopal Attacks Associated With Partial Heart Block, Clifton Med. Bull. **20:** 1, 1936.
5. Wedd, A. M.: Observations on the Clinical Pharmacology of Digitalis, Bull. Johns Hopkins Hosp. **30:** 131, 1919.

Department of Reviews and Abstracts

Selected Abstracts

de Boer, S.: The Effect of Rauwolfine on the Heart and on Fibrillation of the Heart Chambers. Cardiologia **1**: 1, 1937.

The heart rate of frogs, cats, and rabbits decreases after poisoning with rauwolfine.

The refractory period of the frog's heart increases after administration of rauwolfine.

In frogs there are disturbances of the heart rhythm comparable with those following poisoning by digitalis compounds.

Rauwolfine poisoning produces artificial changes of the heart rhythm in the frog.

After poisoning of the frog's heart with rauwolfine the intraventricular conductivity is delayed.

Rauwolfine does not prevent auricular or ventricular fibrillation either in cats or in rabbits. (If there should be any influence at all of rauwolfine on auricular or ventricular fibrillation this would be insignificant.)

AUTHOR.

Martini, P., and Fr. Grosse-Brockhoff: Action of Strophanthin in Fever. Arch. f. exper. Path. u. Pharmakol. **180**: 597, 1936.

Action of strophanthin was determined in rabbits suffering from fever experimentally produced with staphylococcus injections. It was found that these animals gave less response to the drug than normal rabbits.

L. N. K.

Lederer, E.: Capillary Circulation Studies. II. Action of Certain Drugs on the Circulation. Arch. f. exper. Path. u. Pharmakol. **182**: 372, 1936.

Thyroxin subcutaneously causes capillary dilatation and acceleration of flow. Adrenalin and strychnine slow the flow.

L. N. K.

Lissak, K., and Kobas, F.: Symptomatology of Anaphylactic Shock in the Dog and the Mechanism of Its Production. Arch. f. exper. Path. u. Pharmakol. **182**: 504, 1936.

In shock, both anaphylactic and histamine, the blood pressure drops, the spleen shrinks, and the bronchial muscles contract. This occurs even when the adrenals are removed and the spleen is denervated. This indicates a direct humoral action in smooth muscle, as was demonstrated on isolated strips of spleen. The sensitivity of the dog to choline and acetylcholine is increased during sensitization to foreign protein, but the sensitivity to histamine is unchanged.

L. N. K.

Went, S., and Lissak, K.: The Rôle of Choline in the Production of Shock in the Guinea Pig Heart. Arch. f. exper. Path. u. Pharmakol. **182**: 509, 1936.

The guinea pig heart during anaphylactic shock liberates a substance into the perfusate which inhibits the frog's heart. (This inhibition is abolished by atropine.)

This perfusate has no effect on the leech preparation (used as a specific for acetylcholine). The acetylized perfusate works both on the frog heart and on the leech preparation. The choline content of the heart in anaphylactic shock decreases, whereas histamine remains unchanged. The liberated substance, from these studies, is thus shown to be choline.

L. N. K.

Weinberg, J.: Studies of Central Vasomotor Regulation. Part II. Histamin. Arch. f. exper. Path. u. Pharmakol. **185**: 235, 1937.

In trained, previously trephined, unanesthetized dogs, injections of histamine 0.01 to 0.1 mg. into the lateral ventricles gave consistent rises in blood pressure of from 20 to 56 mm. Hg lasting from fifteen to thirty-eight minutes. Twenty injections in all were given to eight dogs. One smoked drum record of the blood pressure obtained as usual from a superficial branch of the saphenous artery is offered. The rise in blood pressure preceded vomiting and defecation and the animals did not appear to be disturbed by the injection. In two instances prolonged fall in pressure followed the rise. The author believes that these studies make it necessary to reconsider Cushing's investigations in man which tended to show that histamine had no effect when given intracranially.

J. M. S.

Ferrannini, A.: Action of Strophanthin on the Purkinje Fibres on the Dog Heart. Arch. internat. de pharmacodyn. et de thérap. **53**: 501, 1936.

The mechanogram optically recorded and the electrogram of isolated Purkinje fibers were studied. It was found that strophanthin increased the amplitude and rate of the beat of the Purkinje fibers and altered the contour of its electrical curve. This drug also leads to arrhythmias, alternans, and contracture.

L. N. K.

Tournade, A., and Chevillot, M.: Is the Action of Vaso-Dilator Nerves Only a Matter of Liberation of Acetylcholine? Compt. rend. Acad. d. sc. **204**: 1586, 1937.

The purpose of this short note is to add to the literature two instances in which the effects of faradization of the nerve of Hering had different effects from injection of acetylcholine. The observations were as follows:

1. The left kidney of Dog I was perfused through the cervical vessels of Dog P. Stimulation of the right nerve of Hering of Dog I was followed, not only by fall in blood pressure and slowing of the heart, but as well by *vasodilatation* of the renal vessels. A similar reaction was obtained with 0.05 mg. acetylcholine injected directly into the renal artery. Then the perfusing Dog (P) received 10 mg. of atropine. Now electrical stimulation of the nerve was followed, as before, by renal vasodilatation while the same dose of acetylcholine was followed by marked vasoconstriction.

2. Injection of 0.5 mg. ergotamine directly into the renal artery resulted in constriction of that organ's vessels and a rise of 5 mm. Hg in the systemic pressure of Dog P. Faradization of the nerve of Hering was now without effect while intra-arterial injection of acetylcholine was followed by *vasodilatation*. When acetylcholine was injected into the saphenous vein of Dog I, fall of blood pressure did not evoke constriction of the renal vessels perfused by Dog P. These two observations suggest that ergotamine has paralyzed vasoconstriction and dilatation due to nervous stimuli, while injection of acetylcholine can still produce vasodilatation.

The authors assert that the theory of humoral transmission of nervous impulses is important, but believe that this mechanism is not the only one for transmission of

nervous impulses. They believe that physical transmission is at least of equal importance. They recall the usual objections to their form of experiment, namely, that amount of acetylcholine and site of liberation may differ from normal.

J. M. S.

Thiel, K.: Action of Artificial Breathing. Med. Klin. 32: 633, 1936.

Dogs were asphyxiated under morphine anesthesia until no flow could be measured in the carotid artery with a Rein stromuhr. The heart was revived by massage and by artificial breathing. While blood flow quickly returned to normal, the electrocardiogram remained abnormal for some time. The use of O_2 rich air did not affect the rate of restoration. Cardiazol and sympatol, however, did.

L. N. K.

Gotsev, T.: Vasomotor Centers I. Pflüger's Arch. f. d. ges. Physiol. 237: 609, 1936.

The author presents the effect of a large number of vasomotor substances determined before and after decapitation of dogs. No difference was noted. The conclusion is arrived at that these vasomotor centers play little rôle in the action of these substances. Among substances used were pituitary derivatives, acetylcholine, lactic acid, ergotamine, caffeine, sodium benzoate, and histamine.

L. N. K.

Gollwitzer-Meier, Kl, Kramer, K., and Krüger, E.: Action of Adrenalin on the Energy of the Heart. Pflüger's Arch. f. d. ges. Physiol. 237: 639, 1936.

Adrenalin (1/200 to 1/100 mg.) increases the gaseous metabolism of the heart about 350 per cent over normal. The peak of gaseous metabolism lags behind the peak of work. Hence, there is an anoxybiotic phase of increased work. The action of adrenalin on gaseous metabolism is decreased in the presence of anoxemia, but unaffected by the level of venous flow and arterial resistance. The increased metabolism is in part brought about by increased coronary flow but chiefly by increased A-V O_2 difference.

L. N. K.

Puddu, V.: The Action of Cardiac Nerves. Pflüger's Arch. f. d. ges. Physiol. 238: 467, 1937.

The author found that there are two phases to the changes in the electrocardiogram following stimulation of the sympathetic nerves in the dog, and further that the right and left nerve have opposite effects on the ventricular complex. Both nerves appear to go to all parts of the hearts. He could not demonstrate that sympathin played any rôle.

Following complete A-V block on cutting both bundles in the dog, vagus stimulation causes a slowing of the idioventricular pacemaker. The author attributes this to liberation of acetylcholine-like substances transported to this part of the heart.

L. N. K.

Sachs, A.: The Effect of Cholin Bodies on Auricular Systole. Cardiologia 1: 74, 1937.

The choline derivatives which were investigated had similar actions. The smallest doses required to diminish the force of auricular contraction were 0.1 acetylcholine, 0.25 doryl, 1 cholinechloride, 50 cholazyl, in 40 c.c. of the fluid in which the auricular

muscle was suspended. Smaller doses increased the force of contraction, and still smaller doses were ineffective. With large doses slowing of the rate of contraction was only observed associated with diminution of force. Frequently, however, the force of contraction was diminished without slowing. No reduction of tonic activity of the auricular muscle was observed. The action of these compounds depends not so much on the absolute amount but on the effective concentration inside the cell. This applies to acetylcholine and doryl, and to a smaller extent to cholinechloride and cholazyl. It is suggested that this explains the variable responses obtained with equal doses on the same auricular strip.

The auricular strip of the rabbit's heart is suitable for the assay of unknown acetylcholine-like compounds in moderate but not in the smallest concentrations.

AUTHOR.

Zimmermann, O.: Pathogenesis of Gonococcal Arthritis, Endocarditis, and Sepsis. Wien. klin. Wchnschr. **49**: 1518, 1936.

A case report is presented with a late involvement of the heart in the form of inflammatory perforation of the aorta through the ventricular septum into the right ventricle. There was a nonarthritic involvement eighteen years after gonorrheal urethral infection and the cardiac complication occurred six years after the joint involvement. This last was associated with mitral, aortic valvulitis, and gonorrheal sepsis. The aortic valvulitis was superimposed on a congenital bicuspid valve with stenosis.

L. N. K.

Holzlöhner, E.: The Respiratory Pulse (Cardiopneumogram) and the Return Flow of Blood to the Heart. I. Its Relation to Posture in Man. Ztschr. f. Biol. **97**: 409, 1936.

A record on a man taken from the air passages during respiratory arrest showed a decrease in lung volume occurring at the onset of ejection of the heart and an increase in lung volume at the end of the ejection period. The latter indicates an augmented venous return flow into the chest greater than arterial outflow, indicating a systolic suction. In the extended posture the suction action is less; in the flexed posture, it is augmented. The greatest suction action occurs on reclining and in deep inspiration.

L. N. K.

Raab, W., and Friedman, R.: The State of the Circulatory Tree in Vegetarians and Alcoholics. Ztschr. f. klin. Med. **130**: 505, 1936.

It was found that alcohol excess has no detrimental effect on arteriosclerosis and hypertension. The avoidance of meat does not check the development of arteriosclerosis but blood pressure and central vasomotor excitability is decreased. This is especially marked if eggs and milk products are also eliminated.

L. N. K.

Fabian, G., and Scriba, J.: The Determination of the Basedow Heart by the Dyspnea Test. Ztschr. f. klin. Med. **130**: 773, 1936.

CO_2 dyspnea is produced and the relation of maximum depth to the rate of breathing is determined. This was done in 33 patients with hyperthyroidism. The older the individual the more heart involvement present; the same relationship holds with regard to the increase in basal metabolism and the duration of the hyperthyroid state.

L. N. K.

Wezler, K., and Goyert, K.: A Method of Demonstrating the Action of the Blood Pressure Regulator Nerves in Man. Ztschr. f. Kreislaufforsch. 29: 241, 1937.

The authors made the tests by determining in optically recorded pulse curves (1) the period of free oscillation of the carotid artery (from the duration of the first dip in the peak of the carotid pulse times 2), (2) the ratio of the pulse wave velocity in muscular arteries (viz. brachial-radial) over that in elastic arteries (viz. aorta-iliac) and (3) the ratio of duration of systole to cycle length in the carotid pulse. The first of these is used as an index of the magnitude of the stimulus. It varied inversely with the endovascular pressure (and hence also inversely with the pulse wave velocity). The second is used as an index of the state of contraction of the muscles in the media of the muscular arteries. The third is used as an index of the reflex action on the heart. A pressure drop in animals causes an acceleration of the pulse and an increase in the systole/cycle ratio. The authors have demonstrated that reflexes operate not only on heart and peripheral blood vessels but also alter the elasticity of the larger arteries. In a single individual where five separate sets of readings were obtained, it was found that as free oscillation in the carotid lengthened, the ratio of pulse wave velocities decreased, the heart accelerated and systole/cycle ratio lengthened. Similar correlations could be made out on comparing a group of normal individuals, but there was a difference between the standing and prone positions. The authors demonstrated that a high sympathetic tone in arteries was associated with a low sympathetic tone in the heart due to reflexes from the blood pressure regulators.

L. N. K.

Tietze, K.: Action of Baths on Circulation Time in Man. Ztschr. f. Kreislaufforsch. 29: 354, 1937.

The method of Matthes and Malikiosis for circulation time was used. It consists of holding the breath as long as possible after taking a breath of a CO_2 rich atmosphere. The O_2 saturation of arterial blood in the ear and the hand is measured by an indirect method in the unopened blood vessels and the time from the first breath until the blood begins to show an increase in O_2 saturation is used as a measure of circulation time from the lung to the ear and from the lung to the arm. Hot baths caused a shortened circulation time and cold baths increased the circulation time. The same effect was produced by cold and hot applications to one extremity. Similar changes with the baths were found in minute volume flow determined by the arteriovenous difference of O_2 (where the venous blood obtained is not stated) using the Fick principle.

L. N. K.

Schlomka, G., and Vienken, W.: Studies on the Physiological Irregularities of the Heart Beat. II. The Relation Between Respiratory Arrhythmias and Respiratory Alterations in Electrocardiographic Configuration. Ztschr. f. Kreislaufforsch. 29: 194, 1937.

The authors determine the type index of the electrocardiogram by the following formula:

$$I = \frac{(O_1 - U_1) - (O_3 - U_3)}{(O + U)\ \text{max.}}$$

where O_1 and O_3 are the magnitudes of the major upright phase of QRS in Leads I and II, U_1 and U_3 are the magnitudes of the major downward phase of QRS in these leads, and (O and U) max. is the sum of the major upright and major inverted phases of QRS in either Lead I or III, depending on which value is the largest. The authors also determined the variation of the type index during the respiratory cycle

by the difference between the inspiratory and expiratory type index. The analysis is based on 38 electrocardiograms. They argue that this index gives evidence of the functional state of the heart. On this basis, they attribute changes in the electrocardiogram during respiration to hemodynamic alterations of the heart. (These interpretations are speculative and need further support.)

L. N. K.

Schlomka, G., and Theiss, O.: Determination of the Relative Duration of Systole. II. Relative Duration of Systole in Hypertension. Ztschr. f. Kreislaufforsch. **29**: 385, 1937.

The correlation factor between the cycle length and the cube root of the Q-T interval was determined in 287 cases. In general the relative duration of systole is longer in hypertensives than in normals, and this lengthening is proportional to the pressure level. Aging causes a lengthening in systole in hypertensives as well as in normals. Further, the range of systolic duration at different heart rates is greater in hypertensives than in normals. The lengthening of systole is viewed by the authors as the result of insufficiency of the heart, which acts to permit a greater output than would otherwise be possible.

L. N. K.

v. Zárday, I.: Unusual A-V Conduction Disturbances. Ztschr. f. Kreislaufforsch. **29**: 208, 1937.

A case of short P-R interval and increased duration of QRS is reported in which precordial leads were used to analyze the disturbances further. These indicated early stimulation of the right and late stimulation of the left ventricle. This is attributed, as has been done previously, to conduction to the right ventricle via the bundle of Kent or some other abnormal junctional bridge. When the heart rate was accelerated, it was found that P-R lengthened and QRS duration shortened but the duration from the beginning of P to the end of QRS was unchanged. This is interpreted as indicating block in the abnormal junctional bridge.

L. N. K.

Steinmann, B.: The Electrocardiogram in Carbon-Monoxide Poisoning. Ztschr. f. Kreislaufforsch. **29**: 281, 1937.

Twenty-one of the thirty cases of carbon-monoxide poisoning showed electrocardiographic evidence of myocardial damage. In nine cases with mild poisoning, no electrocardiographic abnormalities were seen. These changes in the electrocardiogram are reversible. No instance of persistent damage could be demonstrated. The changes were chiefly depression of the S-T segment and flattening of the T-wave. These are attributed to the anoxia.

L. N. K.

Riseman, Joseph E., and Brown, Morton G.: The Sedimentation Rate in Angina Pectoris and Coronary Thrombosis. Am. J. M. Sc. **194**: 392, 1937.

The corrected sedimentation index was studied in 113 persons: 37 with coronary thrombosis, 55 with angina pectoris, and 21 apparently normal persons between the ages of forty-five and seventy.

Elderly individuals, without any evidence of disease, may have a corrected sedimentation index slightly higher (up to 0.70) than the accepted normal for young adults.

A moderate elevation of the corrected sedimentation index (0.73 to 1.38) was found in over half of the patients with angina pectoris. There is reason to believe that attacks of angina pectoris occasionally result in myocardial damage.

An elevated sedimentation rate is one of the most constant manifestations of coronary thrombosis. The fastest rates were observed between the fourth and twelfth days after the onset of symptoms.

In two-thirds of the cases the rate was considerably greater than that seen in angina pectoris; this may be of value in differentiating between angina pectoris and coronary occlusion during the first two weeks after the onset of an attack.

The sedimentation rate reflects the course of the disease and is an aid in following the progress of the patient but is of little or no aid in the prognosis of the acute attack.

The mortality of patients discharged from the hospital with fast sedimentation rates was twice as great during the first year after discharge as that of patients discharged with low or normal rates. It is advisable to continue bed rest until the sedimentation index either returns to normal or shows no further progression towards normal.

AUTHOR.

Palmer, J. H.: The Size of the Heart After Coronary Thrombosis. Canad. M. A. J. 36: 387, 1937.

Enlargement of the heart was found by radiological methods in 64 per cent of a series of 200 patients who had survived an attack of coronary thrombosis. Doubtful enlargement, 16 per cent of the series, was for the purpose of this paper added to the normal group, but the high incidence of enlargement in published necropsies favors the view that these doubtful hearts are in reality enlarged.

The factors causing enlargement after coronary thrombosis are discussed. By far the most important proved to be hypertension, which was held to be the single or predominant cause in more than 80 per cent of all cases with enlargement.

Disease of the coronary arteries, either the actual thrombosis with its resulting infarction or the underlying arteriosclerosis, led to increase in the size of the heart in a total of 11 cases (8.6 per cent). Of these, 4 (3.1 per cent) had cardiac aneurysm, 3 (2.4 per cent) had a bundle-branch lesion, and the remaining 4 (3.1 per cent) had enlargement, apparently due to chronic myocardial ischemia alone.

No example of so-called acute dilatation of the heart was discovered among 27 patients examined radiologically within a month of the attack. Congestive failure, which was not seen in hearts of normal size, seldom led to an appreciable increase in the degree of enlargement.

About one-third of the patients (36 per cent) failed to show or to develop enlargement, though watched over periods averaging more than three years following the first attack of coronary thrombosis; and this number included several with recurrent attacks.

AUTHOR.

Palmer, J. H.: The Prognosis Following Recovery From Coronary Thrombosis, With Special Reference to the Influence of Hypertension and Cardiac Enlargement. Quart. J. Med. 6: 49, 1937.

The prognosis, with special regard to the influence of hypertension and cardiac enlargement, has been studied in 212 cases of coronary thrombosis which survived the attack by three months.

More than one-fourth were able to lead fairly active lives. In the remainder, angina of effort and dyspnea on exertion (including chronic congestive failure) were the most important symptoms causing restriction of activity or invalidism, and these were operative in almost equal proportion. The active group lived longer following the attack than the restricted.

The onset and incidence of angina after coronary thrombosis were not related to the height, or changes in the height, of the blood pressure, or to the size of the heart. Angina of every grade of severity, including that compatible with a fairly active life, occurred in 39 per cent of cases prior to the attack and in 58 per cent of cases following it; in less than 10 per cent did prior angina fail to recur after the attack. The presence of subsequent angina did not affect the average duration of life.

The incidence of dyspnea severe enough to cause restriction of activity followed closely the incidence of cardiac enlargement. Hypertension was not more frequent in the dyspneic group than in the whole series.

Congestive failure, which affected 13 per cent of the series, was found only in patients with enlarged hearts.

Subsequent attacks of coronary thrombosis occurred in 28 per cent, about half of them during the first two years. The incidence of these attacks was unrelated to the height of the blood pressure, but was somewhat higher in cases with enlargement than in those with hearts of normal size. About one-fifth of these subsequent attacks were fatal.

The duration of life following the attack averaged 4.2 years in 65 cases known to have died. Hypertensives appeared to have a somewhat more favorable outlook in this regard than nonhypertensives. The groups with cardiac enlargement and with congestive failure showed a slight reduction in the duration of life, which was, however, unaffected in the average by further attacks of coronary thrombosis.

A statistical table is presented showing the rate of survival based on experience of the series.

Short summaries are given of the histories of eleven patients (5 per cent of the series) known to have lived for more than ten years following the attack.

Blood pressure changes and the height of the blood pressure following recovery from an attack of coronary thrombosis are on the whole of little significance.

Cardiac enlargement is a most important factor in causing restriction of activity; the expression of its influence is dyspnea on exertion, and in the most severe cases congestive failure.

The probability that following recovery from an attack of coronary thrombosis a patient will be able to lead a fairly active life is almost twice as great in those with normal sized hearts as in those with cardiac enlargement.

AUTHOR.

Kisch, Bruno: Interpolated Ventricular Extrasystoles. Cardiologia 1: 88, 1937.

Report of records of a case with interpolated ventricular extrasystoles. The delayed conductivity of the contraction following the interpolated systole is the greater when (a) the general conductivity in the heart is less efficient, and (b) when the time between extrasystole and the following contraction is less.

The delayed conductivity following an interpolated extrasystole is the same phenomenon as in what is known as "Wenckebachsche Perioden." The occurrence of the preventricular wave (described in an earlier paper as "Zwischenzacke") in the electrocardiogram of a heart beat with greatly delayed conductivity is further evidence that these preventricular waves ("Zwischenzacken") are significant of abnormal conductivity.

AUTHOR.

Bernheim, Alice R., and London, Isabel M.: Arteriosclerosis and Thrombo-angiitis Obliterans: Report of Cases and Treatment. J. A. M. A. **108**: 2102, 1937.

Ninety-nine cases of arteriosclerosis of the extremities and 54 cases of thrombo-angiitis obliterans were treated. Relief of vasospasm was considered important, because it is an underlying process in both diseases. Treatment of vasospasm consisted in the use of measures to eliminate the following causes: tobacco, improper diet, worry, undue physical exertion, and cold. An increase in blood viscosity was found in patients with arteriosclerosis as well as in those with thrombo-angiitis obliterans. For this reason, sodium citrate was given in all cases presenting severe symptoms. Decreases in viscosity of from 1 to 2 points followed the intravenous injection of 250 c.c. of a 2 per cent solution of sodium citrate. There was improvement in 83 of the cases of arteriosclerosis, and in 43 of the cases of thrombo-angiitis obliterans.

H. M.

Allen, Edgar V., and Crisler, George R.: The Result of Intra-Arterial Injection of Vasodilating Drugs on the Circulation: Observations on Vasomotor Gradient. J. Clin. Investigation **16**: 649, 1937.

The vasodilating drugs, papaverine hydrochloride, acetyl B-methylcholine (mecholyl), and histamine, cannot be "fixed" in an extremity to any great degree by injecting them into the lumina of arteries supplying the extremities. For example, the results on the temperature of the toes of the right foot of injecting mecholyl into the right femoral artery are about the same as those which follow the injection of mecholyl into the brachial artery.

The lower extremities contrasted to the upper extremities are relatively very refractory to vasodilating agents, as shown by the fact that the vasodilating drugs used produced moderate to marked increases in temperatures of the fingers and no increase or very little increase in the temperatures of the toes regardless of whether papaverine and mecholyl were injected into the femoral artery, into the brachial artery, or intravenously or intramuscularly. This refractoriness of vasodilatation in the lower extremities seems intimately associated in some way, as yet unexplained, with the much higher incidence of chronic occlusive arterial diseases in the lower extremities as contrasted with the incidence in the upper extremities.

AUTHOR.

Springorum, W.: The Influence of Local Thermal Stimulation Upon the Flow of Blood Through the Skin. Arch. f. d. ges. Physiol. **238**: 517, 1937.

By placing a small Rein stromuhr on the artery leading to the ear of a dog, a technique previously described by the author and abstracted a few months ago in this journal, Springorum was able to follow changes in the flow of blood to the ear while immersing it in cold or hot baths. He studied this problem anew because most of the methods for estimating change in blood flow to the skin have been indirect ones while this is direct.

Large dogs were lightly anesthetized, usually with morphine pernocton, sometimes with chloralose. The drug used for anesthesia made little difference but as anesthesia was gradually deepened the reaction to heat was first lost, then that to cold.

The importance of the work lies in the quantitation of the reactions and the timing of their appearance following the stimulus through the use of optical records of unusual excellence. The results are somewhat as follows: (1) Increase in flow on raising the temperature from 20° to 40° is about four to six times. Decrease

in flow from room temperature to 13° may amount almost to complete stoppage. (2) Repeated application of heat tends to reduce progressively the speed of development of and ultimate height of the reaction. (3) Many times reactions to heat were slight and occasionally even absent. The circumstances under which these failures occurred were not quite clear to the author. The reaction to cold was apparently more constant. (4) The increase in flow of blood in response to warmth begins after a latent period of ten to twenty seconds and takes place very abruptly. Decrease in flow with cold begins at once and progresses slowly and steadily.

The author concludes, therefore, that the one reaction cannot be thought of as the reversal of the other and that the mechanisms of inducing the responses must consequently be quite different. He can say nothing about denervated preparations since he was unable to verify completeness of denervation. The carrying out of this procedure would seem a useful complement to the present work. He concludes tentatively that nervous elements must play a large part in regulating the reactions to local thermal stimuli.

J. M. S.

Müller, A.: Thrombophlebitis and Its Treatment With Ambulant Compression Bandages. Med. Klin. 33: 793, 1937.

The author discusses the parts played by local inflammation and slowing of the blood stream in thrombosis and appears to believe that slowing of the stream is more important. After reviewing literature of figures on the outcome of phlebitis, it became apparent that the use of Fischer's compression bandage gave better results and he therefore began to use it. Out of several hundred patients, 85 were thromboses of the deep veins, and 12 were postoperative. Only 2 deaths occurred, both with pulmonary infarcts. The author states that long standing cases with considerable edema and induration often cleared up in a very short time—two to five days—with almost immediate disappearance of pain. He emphasizes the fact that it can be applied over ulcers to great advantage and appears to be especially useful in aborting early painful thromboses.

The rationale is making smaller the venous cross-section and therefore the flow of blood more rapid. He recommends the use of stiff sized cloth for compression bandages wrapped over softer supporting bandages and wads of padding for the bony prominences of foot and tibia. The knee is left free except perhaps for stockinette and the thigh is bandaged tightly with an elastic bandage. The compression bandage must be as tightly wrapped as possible without stopping arterial flow. Unless there are other contraindications the patient is kept up and active.

J. M. S.

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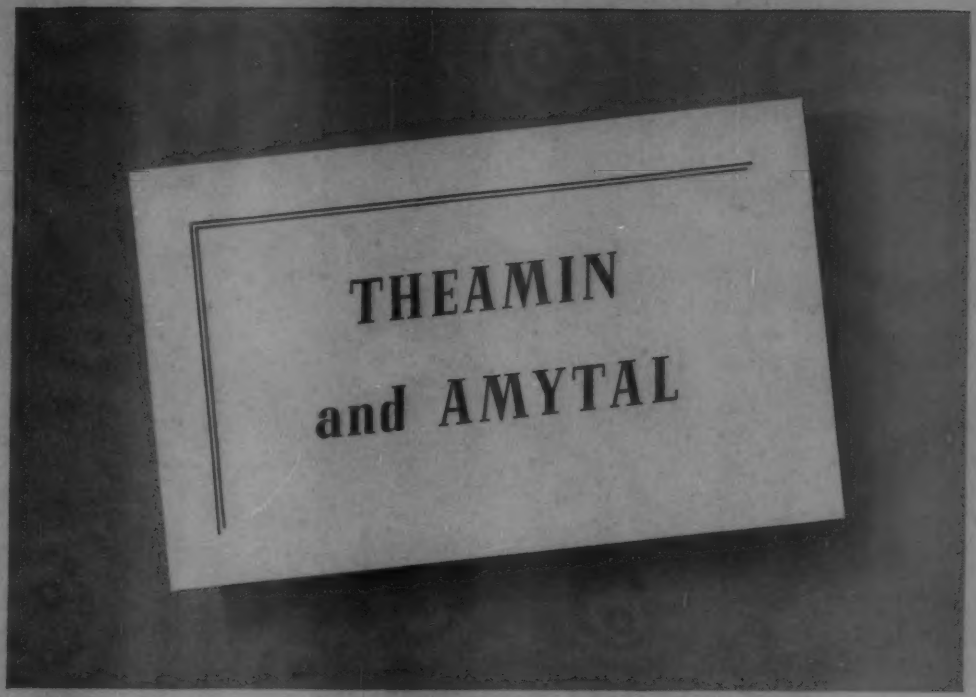

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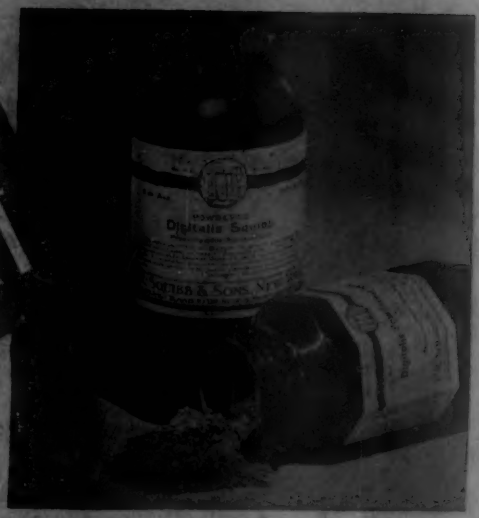

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